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(54) TRIFLUOROMETHYLPYRROLOINDOLE CARBOXYLIC ESTER DERIVATIVE AND PROCESS FOR PRODUCING THE SAME

TRIFLUOROMETHYLPYRROLOINDOLCARBONSÄURE UND DESSEN ESTERDERIVAT SOWIE EIN VERFAHREN ZU SEINER HERSTELLUNG

DERIVE D'ESTER CARBOXYLIQUE DE TRIFLUOROMETHYLPYRROLOINDOLE ET PROCEDE POUR SA FABRICATION

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(56) References cited:
JP-A- 3 128 379
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JP-A- 4 117 383

- **WARPEHOSKI A. ET AL.: 'Stereoelectronic Factors Influencing the Biological Activity and DNA Interaction of Synthetic Antitumor Agents Modeled on CC-1065' J.MED.CHEM. vol. 31, 1988, pages 590 - 603**

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

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Description

[0001] The present invention relates to novel antibacterial and antineoplastic 7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylic acid ester derivatives, 6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylic acid ester derivatives, optically active isomers thereof, and pharmaceutically acceptable salts thereof.

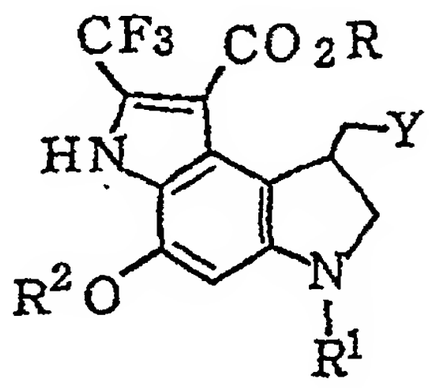
[0002] CC-1065 is disclosed as an antibacterial and antineoplastic antibiotic in J. Antibiotics, 31 1211 (1978) and ibid, 34 1119 (1981); and USP 4169888. Further, duocarmycin A having a similar structure thereto and analogues thereof are disclosed in WO87/06265, EP0318056, J. Antibiotics 42 1229 (1989), and JP-A-4-99774.

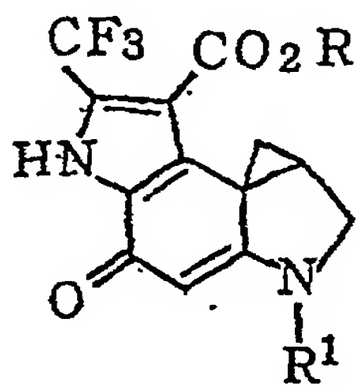
[0003] Further derivatives of CC-1065 are disclosed in JP-A-60-193989, and Japan Patent Kohyo 2-502005. Derivatives of duocarmycins are disclosed in JP-A-3-7287, JP-A-3-128379, EP0354583, and EP0406749. All of these compounds are derived by utilizing the base skeleton of an unmodified natural substance or by modifying chemically a natural substance.

[0004] The clinical therapy of cancer includes surgical excision, X-ray radiotherapy, pharmacotherapy using a chemotherapeutic agent(chemotherapy), and so forth. Of these therapies, chemotherapy is the one and only therapy for cancer having wide-spread metastasis in several body regions and for cancer at the terminal stage. Originally, chemotherapy is expected to be the least to burden a patient, while in fact, chemotherapeutic agents hitherto known impose severe strain on patients due to strong adverse reactions. Further, there are several effective chemotherapeutic agents against leukemia which grows rapidly, but most of them are less effective against a solid tumor which grows slowly. For these reasons, chemotherapy so far is not always primarily adopted for cancer.

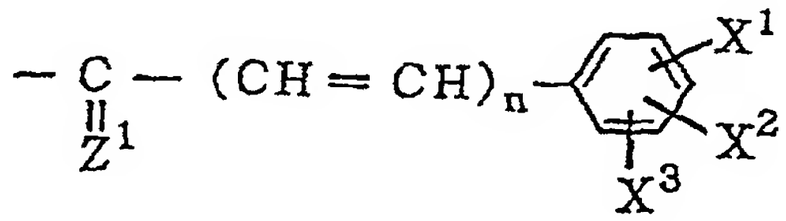
[0005] In view of the present status of the chemotherapeutic agents, the inventors of the present invention have conducted comprehensively the investigation on compounds which exhibit high selectivity to cancer cells and exhibit high efficacy also on solid tumor with less toxicity.

[0006] It was found by the inventors of the present invention that the trifluoromethylpyrroloindolecarboxylic acid ester derivatives represented by the general formula (1) and (2) below, optical isomers thereof, and pharmaceutically acceptable salts thereof exhibit excellent antibacterial effects and antineoplastic effects, and further has high selectivity to cancer cells with low toxicity:

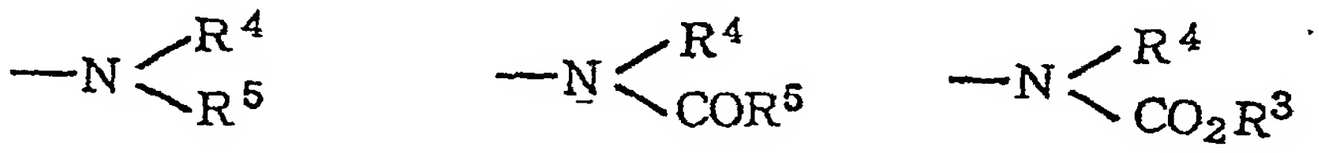
(1) 

(2) 

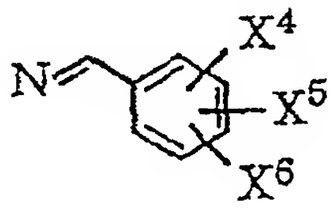
[In the formulas,
R is an alkyl group of $C_1 \sim C_4$,
R^1 is selected from the group consisting of

a. 

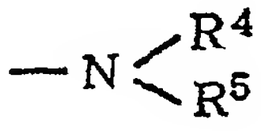
(X^1, X^2, and X^3 are independently a hydrogen atom, OH, OR^3
(R^3 is a linear or branched alkyl group of $C_1 \sim C_6$, $OCOR^3$ (R^3 is the same as above), CHO, NO_2,



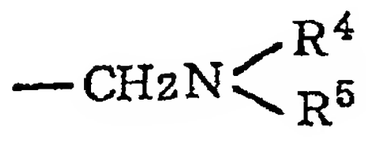
(R^4 and R^5 are independently a hydrogen atom, a linear or branched alkyl group of $C_1 \sim C_6$ (R^3 is the same as above)),



(X^4, X^5, and X^6 are independently a hydrogen atom, OR^3, or



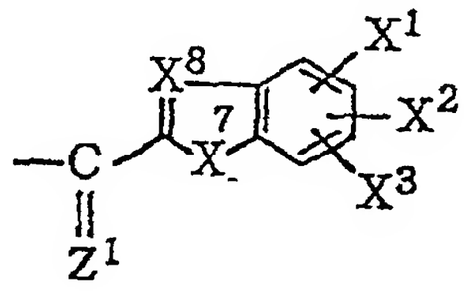
(R^3, R^4, and R^5 are the same as above)),



(R^4, and R^5 are the same as above),

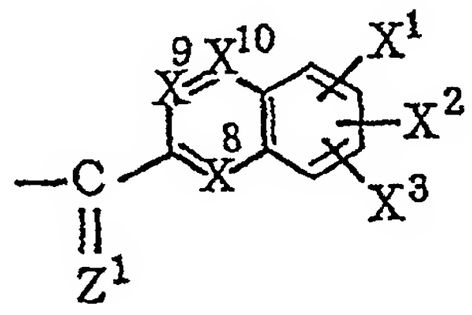
(R^4, and R^5 are the same as above), Z^1 is O, S, or NR^4 (R^4 is the same as above), n is 0 ~ 2),

b.



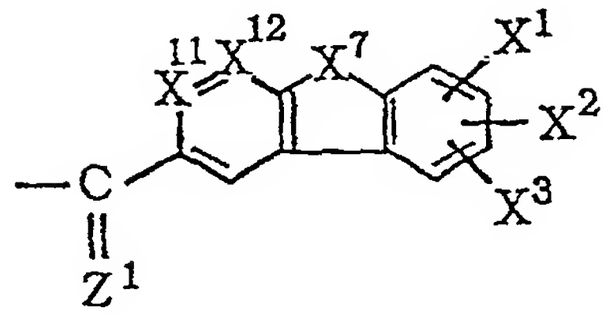
(X^7 is O, S, or NH, X^8 is CH or N (X^1, X^2, X^3, and Z^1 are the same as above)),

c.



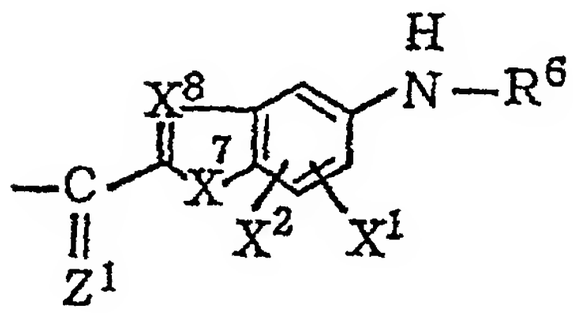
(X^9, and X^{10} are independently CH or N (X^1, X^2, X^3, X^8, and Z^1 are the same as above)),

d.



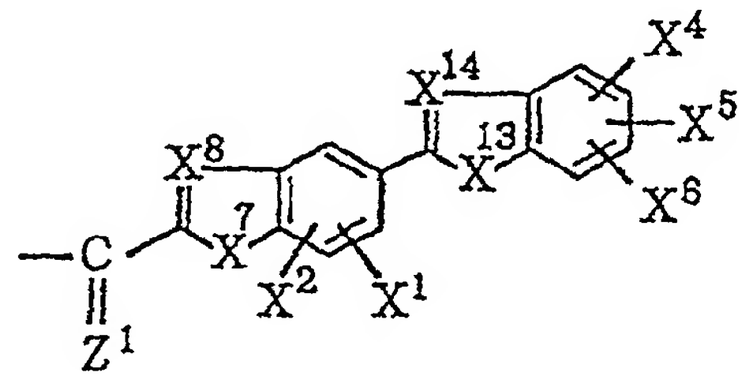
(X11, and X12 are independently CH or N (X1, X2, X3, X7 and Z1 are the same as above)),

e.



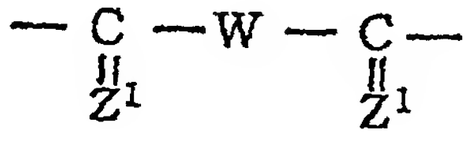
(R6 is represented by the above formula a, b, c, or d (X1, X2, X7, X8, and Z1 are the same as above)

f.

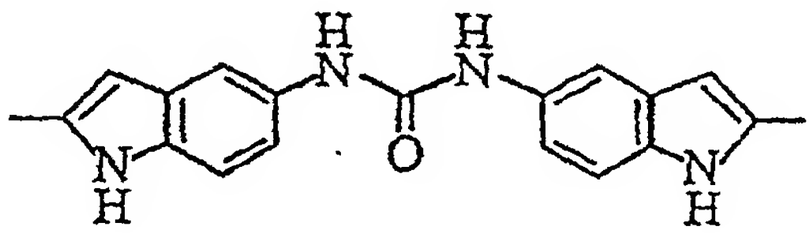


(X13 is O, S, or NH; X14 is CH or N (X1, X2, X4, X5, X6, X7, X8, and Z1 are the same as above)), and

g.



(W is $-(CH_2)_m-$, $-(CH_2)_m-Z^2-(CH_2)_n-$, or



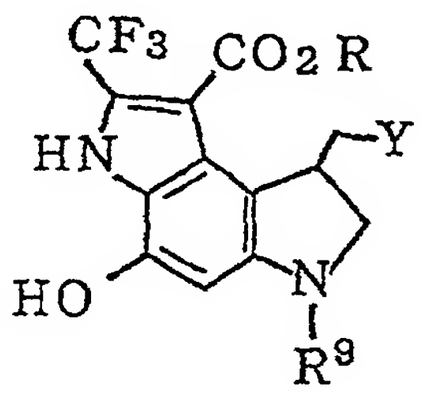
(Z1 is the same as above), Z2 is S, O, or NH, and m and n are independently 0 ~ 16);
R2 is a hydrogen atom, a protecting group for a hydroxyl group, or a biologically decomposable substituent; and
Y is a halogen atom].

[0007] The protective group for an amino group herein includes linear or branched lower alkoxycarbonyl groups of 2 ~ 7 carbons such as methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl, and t-butoxycarbonyl; haloalkoxycarbonyl groups such as 2,2,2-trichloroethoxycarbonyloxy, and 2,2,2-trichloro-1,1-dimethylethoxycarbonyl; and substituted or unsubstituted aralkyloxycarbonyl groups such as benzyloxycarbonyl, and 4-methoxybenzyloxycarbonyl. The protective group for the hydroxyl group includes lower alkyl groups of C_1 ~ C_4 such as methyl and ethyl; and substituted or unsubstituted aralkyl groups such as benzyl, 4-methoxybenzyl, 2,4-dimethoxybenzyl, benzhydryl, and trityl. A bio-

logically decomposable substituent is capable of giving a hydroxyl group by decomposition in an organism and includes lower alkanoyl groups, aryloyl groups, lower alkoxycarbonyl groups, substituted or unsubstituted aryloxycarbonyl groups, α-amino acid acyl radicals; substituted or unsubstituted carbamoyl groups such as N-(lower alkyl)carbamoyl, N,N-di(lower alkyl)carbamoyl, and N-arylcarbamoyl; substituted or unsubstituted pyrrolidinocarbonyl groups such as pyrrolidinocarbonyl, and 3-(dimethylamino)pyrrolidinocarbonyl; substituted or unsubstituted piperidinocarbonyl groups such as 4-(dimethylamino)piperidinocarbonyl, and (4-piperidinopiperidino)carbonyl; substituted or unsubstituted 1-piperazinylcarbonyl groups such as (4-methyl-1-piperazinyl)carbonyl, [4-[2-(dimethylamino)ethyl]-1-piperazinyl]carbonyl, [4-(2-hydroxyethyl)-1-piperazinyl]carbonyl, and [4-[2-[2-(dimethylamino)ethoxy]ethyl]-1-piperazinyl]carbonyl; substituted or unsubstituted 1-morpholinocarbonyl groups; aryl- or alkyl-substituted silyl groups.

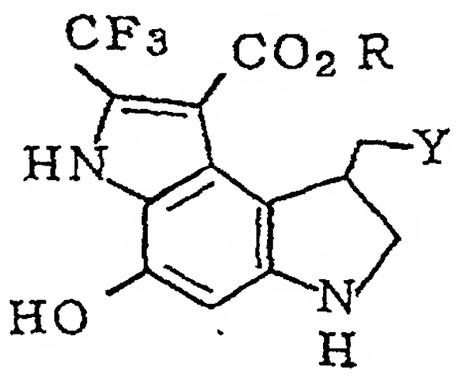
[0008] The compound represented by the general formula (1) or (2) can be produced through the process described below according to the present invention.

[0009] The compound represented by the general formula (3a):



(3a)

(where R^9 is a protecting group for an amino group (R and Y are the same as shown above)) is converted by deprotection to the compound represented by the general formula (3b) below:



(3b)

(where R and Y are the same as above),
or a salt thereof. This deprotection reaction may be carried out by a known method such as the method described in "Protective Groups in Organic Synthesis" 2nd Ed., pp. 315-348 (1990).

[0010] For example, in the case where R^9 is a t-butoxycarbonyl group, the reaction is conducted in an ethyl acetate solution containing 3N hydrogen chloride at a temperature of from 0°C to 50°C, preferably at room temperature for 10 minutes to 2 hours, and the solvent is removed by distillation to obtain the compound of the general formula (3b) in a form of hydrochloride salt with a high purity.

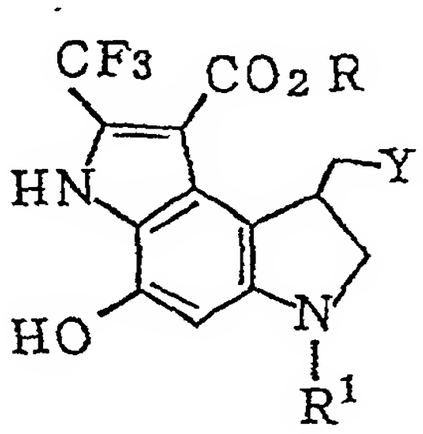
[0011] Subsequently, the compound represented by the general formula (3b) or its salt is reacted with a compound represented by the general formula (5a):

$$R^1\text{-}V \qquad (5a)$$

(Where V is a reactive group such as a halogen atom, a 1-imidazolyl group, a 4-nitrophenoxy group, and a succinimidoyloxy group or OR^1 (R^1 is the same as above): the compound (5a) being a halide of a carboxylic acid or thiocarboxylic acid, an imidazolide of a carboxylic acid or thiocarboxylic acid, an active ester of a carboxylic acid or thiocarboxylic acid, a mixed or symmetric acid anhydride of a carboxylic acid or a thiocarboxylic acid or an imidoyl derivative, e.g., imidoyl chloride, or the compound is condensed with a carboxylic acid represented by the general formula (5b):

R^1-OH (5b)

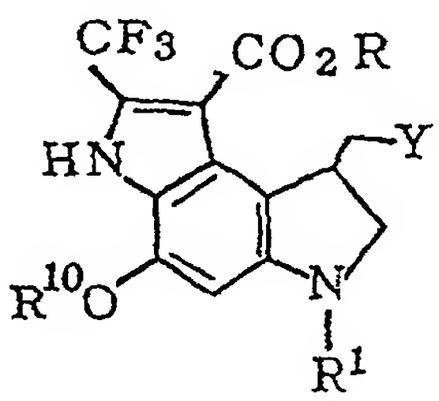
(where R^1 is the same as above) in the presence of a condensing agent such as dicyclohexylcarbodiimide (DCC) and 3-ethyl-1-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI). Thereby, a compound is prepared which is represented by the general formula (3c):



(3c)

(where R, R^1, and Y are the same as above). This condensation reaction is readily allowed to proceed in the presence or the absence of an organic base, e.g., triethylamine, diisopropylethylamine, pyridine, dimethylaminopyridine, etc., or an inorganic base, e.g., sodium hydrogencarbonate, and potassium carbonate in a solvent, e.g., methylene chloride, toluene, acetonitrile, N,N-dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, etc., or a mixture thereof at a temperature of -20 ~ 50°C for 30 minutes to 48 hours.

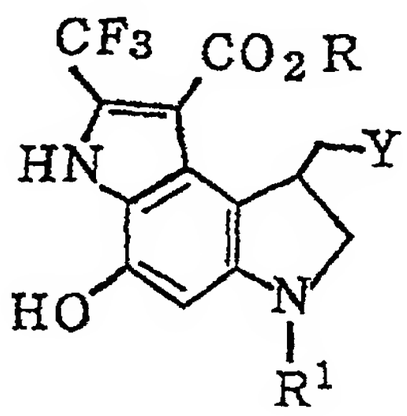
[0012] The compound represented by the general formula (3c) can be converted to a prodrug represented by the general formula (3d):



(3d)

(where R^{10} is a biologically decomposable substituent (R, R^1, and Y are the same as above)) by treatment with a lower alkanoyl chloride, an aryloyl chloride, a lower alkoxycarbonyl chloride, an aryloxycarbonyl chloride, an acid chloride of α-amino acid, a substituted or unsubstituted carbamoyl chloride, or an active ester thereof. This reaction is conducted in the presence or the absence of an organic base, e.g., triethylamine, diisopropylethylamine, pyridine, dimethylaminopyridine, etc., or an inorganic base, e.g., sodium hydrogencarbonate, potassium carbonate, etc. in an inert solvent at a temperature of -20 ~ 100°C, preferably 0 to 50°C.

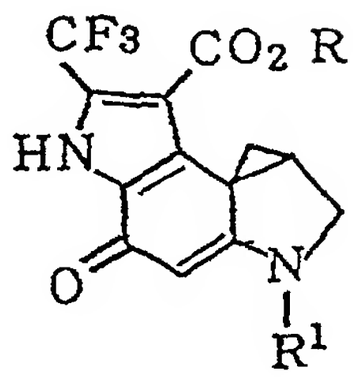
[0013] Further, the aforementioned compound represented by the general formula (3c):



(3c)

(where R, R^1, and Y are the same as above) can be converted by ring closure in the presence of a base to a compound

represented by the general formula (2) :

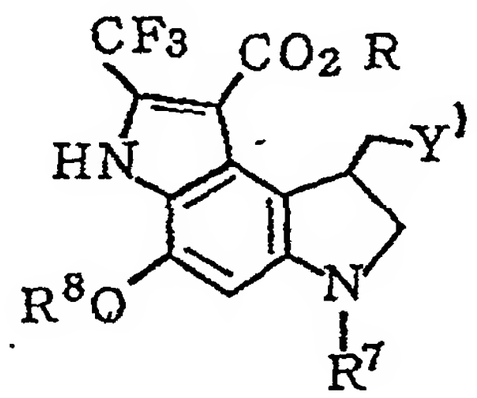


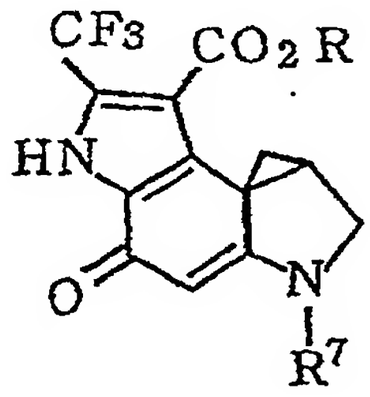
(2)

(where R, and R_1 are the same as above).

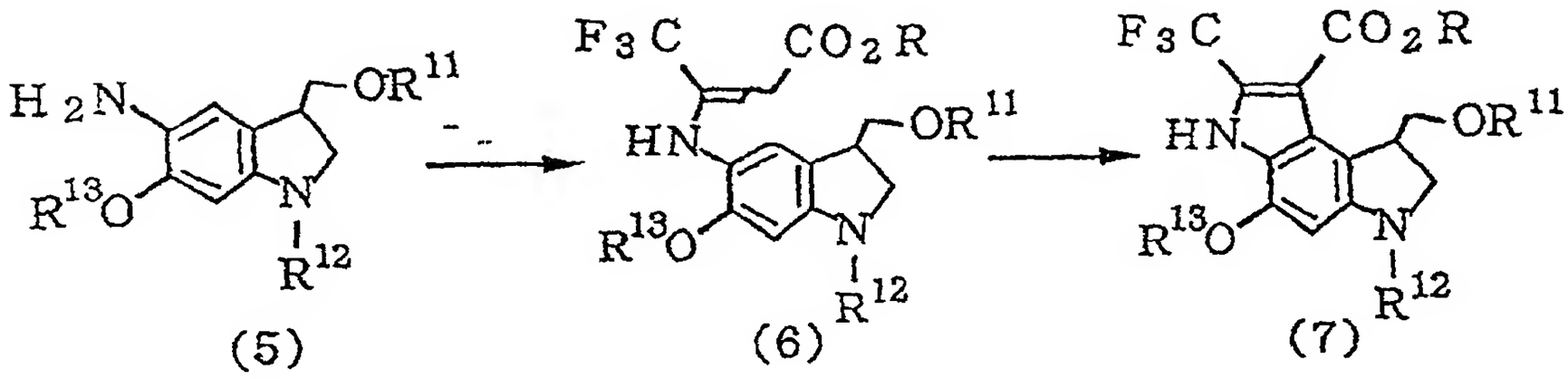
This reaction can be conducted by reacting the above compound (3c) with 1 ~ 10 equivalent moles, preferably 1 ~ 5 equivalent moles of an organic base, e.g., diazabicyclic base, triethylamine, etc. or an inorganic base, e.g., sodium hydroxide, sodium hydride, potassium carbonate, etc. in an inert solvent e.g., dimethylformamide, acetonitrile, tetrahydrofuran, methylene chloride, etc. or a mixture thereof at -78 ~ 100°C, preferably 0 ~ 50°C for 10 minutes to 24 hours, preferably 20 minutes to 5 hours. Furthermore, the above compound represented by the general formula (2) can be converted to the compound represented by the above general formula (3c) by treatment thereof in the presence of an acid, e.g., hydrogen chloride, hydrogen bromide, hydrochloric acid, hydrobromic acid, 20 minutes acid, benzenesulfonic acid, methanesulfonic acid, trifluoromethanesulfonic acid, hydrazoic acid, etc. in an inert solvent, e.g., ethyl acetate, methylene chloride, alcohol, acetonitrile, dimethylformamide, etc. at a temperature of from -20°C to the boiling point of the solvent, preferably 0 ~ 50°C. For this reaction, an excessive amount of the acid is preferably used to shorten the reaction time.

[0014] The compounds which are the starting substances of the present invention represented by the general formulas (3) and (4) are important intermediates:

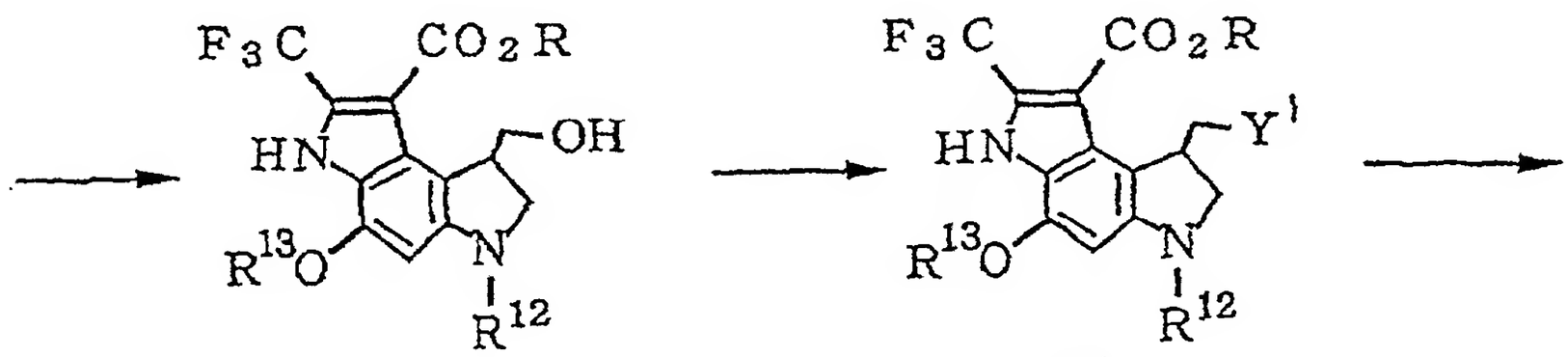
(3) 

(4) 

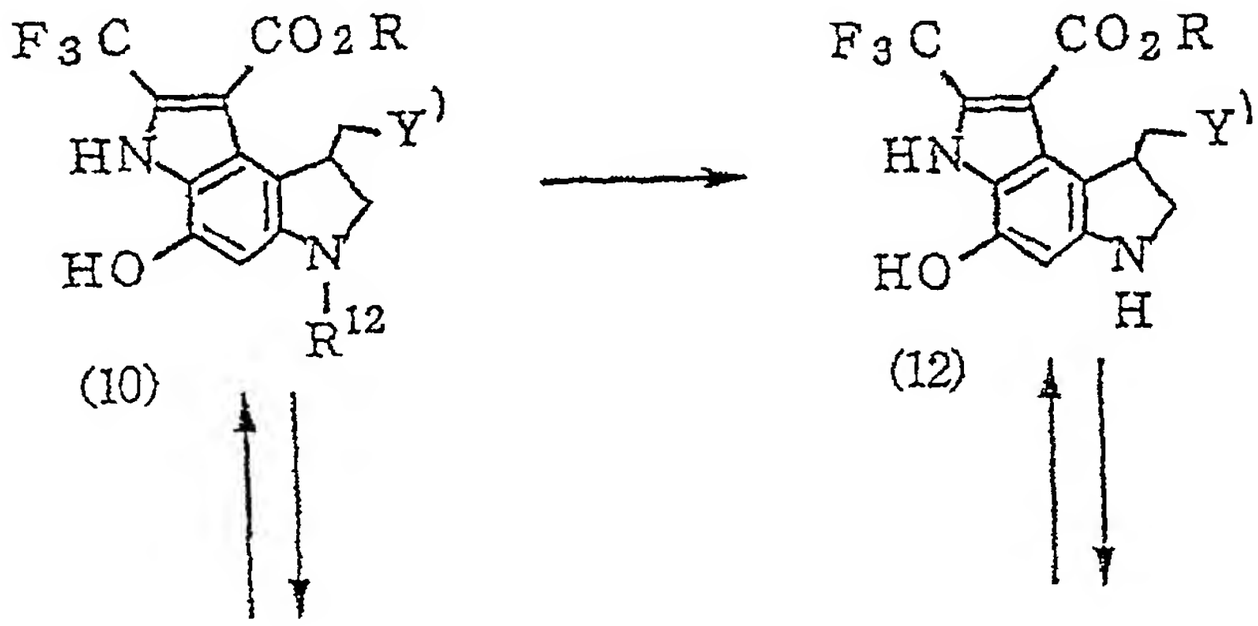
(where R^7 is a hydrogen atom, or a protective group for an amino group, R^8 is a hydrogen atom or a protective group for a hydroxyl group Y' is a hydroxyl group, a protective group for a hydroxyl group or a halogen atom (R is the same as above)), and can be produced by the processes below.



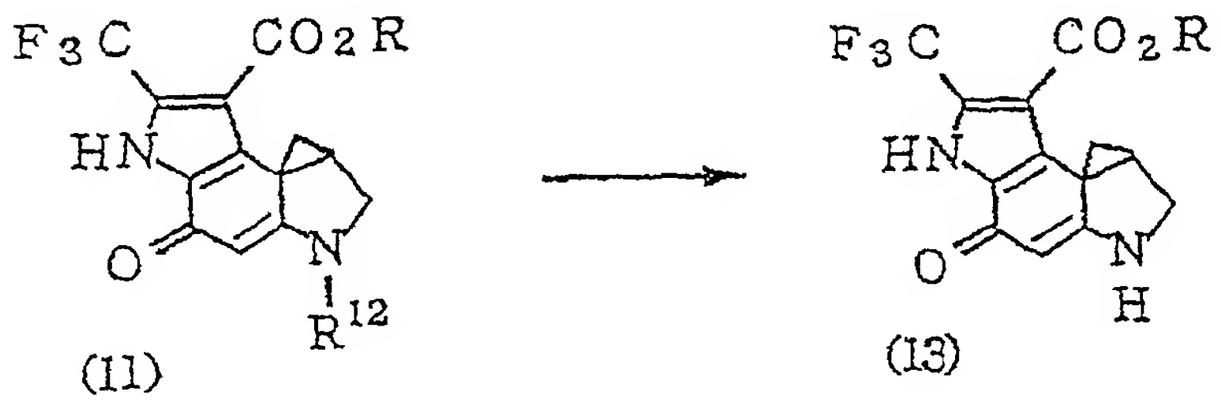
(5) (6) (7)



(8) (9)



(10) (12)



(11) (13)

(where R^{11} is a protective group for the hydroxyl group, R^{12} is a protective group for the amino group, and R^{13} is a protective group for the hydroxyl group (R, and Y' are the same as above)

[0015] Optically active isomers of the compounds of the general formula (1) or (2) can be produced by use of optically active isomers of the compound represented by the general formula (5). The optically active isomers of the compound of the general formula (5) can be obtained by optical resolution after conversion to diastereomers according to the method described, for example, in Journal of American Chemical Society, Vol. 112, p. 5230 (1990). In another method, the alcohol derivative represented by the general formula (8) is converted to diastereomeric esters of an optically active carboxylic acid, and is subjected to optical resolution to obtain an optically active intermediate. The compound represented by the general formula (1) or (2) are useful singly or in combination with a pharmaceutically acceptable additive for antibacterial and antineoplastic agent.

[0016] For example, the compound represented by the general formula (1) or (2) is dissolved in physiological saline

or an aqueous solution of glucose, mannitol, lactose, or the like to provide a medicinal composition suitable for injection.

[0017] In another example, a salt of the compound of the general formula (1) or (2) is freeze-dried in a conventional manner and is mixed with sodium chloride or the like to prepare a readily soluble powder for obtaining an injectable solution. This medicinal composition may contain, if necessary, an additive known in the medicine field, for example, a pharmaceutically acceptable salt.

[0018] The oral medicine includes tablets, capsules, powders, granules, ampules, and the like, which may contain a medicinal additive known in the medical preparation field. If desired, this medicine may be used for intraarterial medication, intraperitoneal medication, intrapleural medication, and so forth.

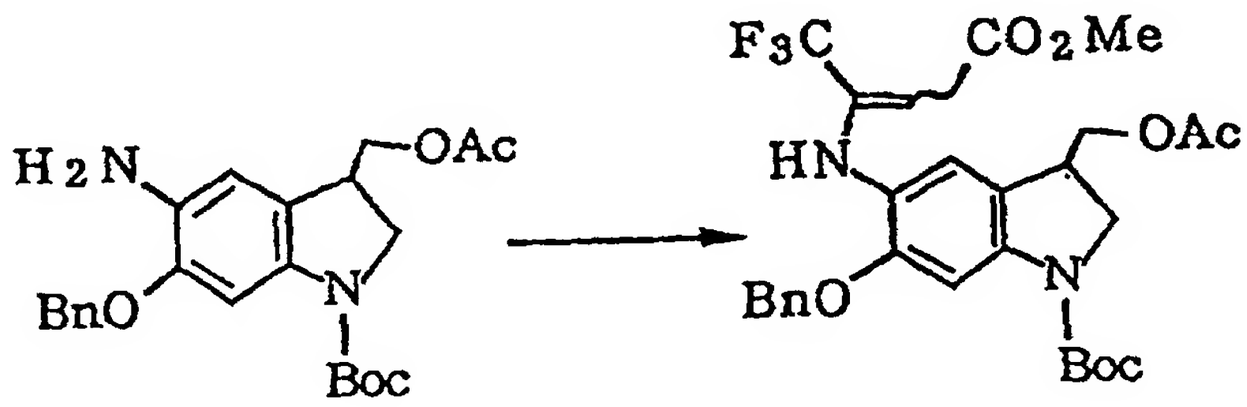
[0019] The amount of the doses differs depending on the age of the patient, the symptom, etc., and usually 0.00001 to 100 mg/kg/day for mammals including humans. The dose is given, for example, once or several times a day, or intermittently 1 to 4 times a week, or once for 2 to 4 weeks.

BEST MODE FOR PRACTICING INVENTION

[0020] The present invention is described below in detail by reference to examples without limiting the invention in any way.

(EXAMPLE 1)

[0021]



[0022] Into 0.2 ml of methanol, was dissolved 41.2 mg (0.1 mmol) of 3-acetoxymethyl-5-amino-6-benzyloxy-1-t-butoxycarbonyl-2,3-dihydro-1H-indole. Thereto, 16.7 mg (0.11 mmol) of methyl 3-trifluoromethylacetylenecarboxylate was added dropwise under ice cooling. After 15 minutes, the reaction mixture was brought to room temperature. After one hour, the solvent was distilled off. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 2 : 1). Thereby, methyl 3-(3-acetoxymethyl-6-benzyloxy-1-t-butoxycarbonyl-2,3-dihydro-1H-indol-5-yl) amino-3-trifluoromethylacrylate was prepared in a crystal form in pale cream color in a yield of 54.7 mg (97 %).

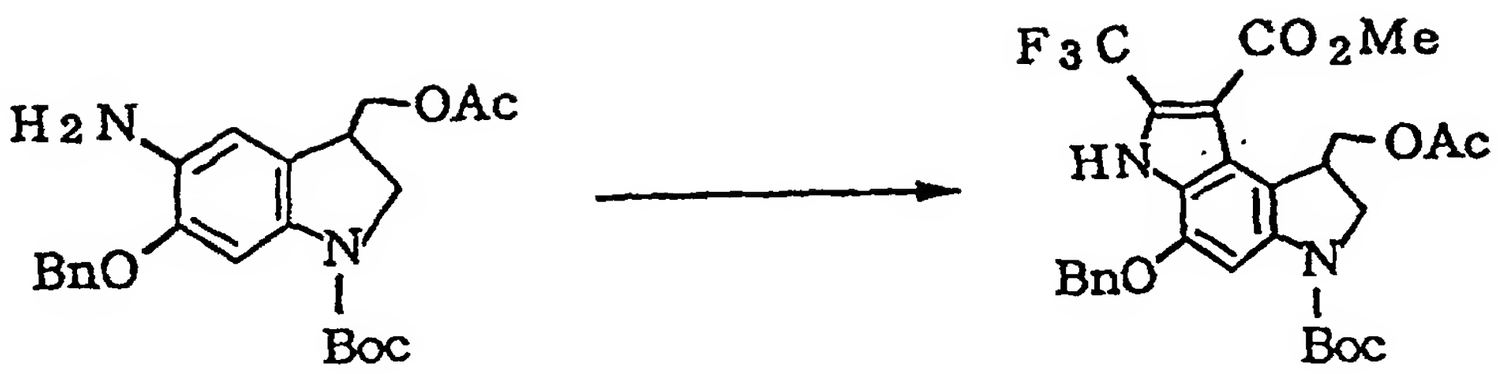
m.p. 114 ~ 115°C

Analysis: $C_{28}H_{31}F_3N_2O_7$			
	C	H	N
Calculated	59.57	5.53	4.96
Found	59.48	5.45	4.88

NMR ($CDCl_3$) δ: 1.56(9H,s),2.08(3H,s),3. 57(1H,m), 3. 72(3H,s),3.78(1H,br),4.06-4.18(3H,m),5. 09(2H,s), 5. 32 (1H,s),7. 08(1H,s),7.29-7.39(5H, m),7. 70(1H,br,s), 9. 51(1H,s)

(EXAMPLE 2)

[0023]



[0024] A crude acrylic acid derivative was prepared in the same manner as in Example 1 from 1.031 g (2.5 mmol) of 3-acetoxymethyl-5-amino-6-benzyloxy-1-t-butoxycarbonyl-2,3-dihydro-1H-indole and 418.2 mg of methyl 3-trifluoromethylacetylenecarboxylate. This crude acrylic acid derivative was heated with 1.122 g (5 mmol) of palladium acetate in 250 ml of N,N-dimethylacetamide at 70°C for 3.5 hours. The reaction mixture was poured onto ice, and thereto 200 ml of ethyl acetate/toluene (1 : 1) was added. The insoluble matter was removed by filtration. The organic layer was washed with watery and was dried over anhydrous sodium sulfate. Thereafter, the solvent was distilled off. The obtained residue was purified by silica gel column chromatography (hexane : ethyl acetate = 3 : 1). Thereby, methyl 1-acetoxymethyl-5-benzyloxy-3-t-butoxycarbonyl-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared in a colorless crystal state in a yield of 815.1 mg (58 %).

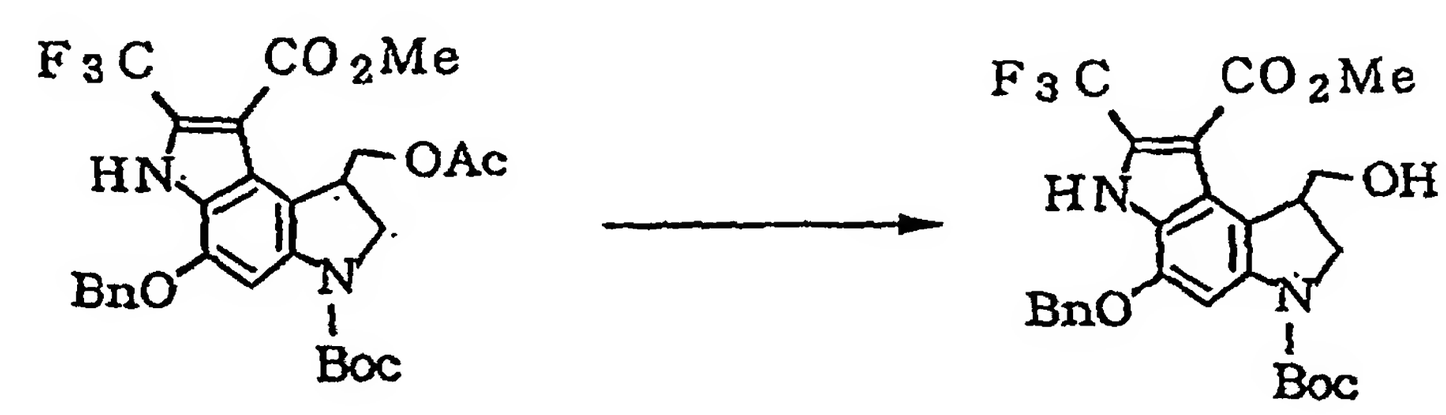
m.p. 156.5 ~ 157.5°C

Analysis: $C_{28}H_{29}F_3N_2O_7$			
	C	H	N
Calculated	59.78	5.20	4.80
Found	59.66	5.11	5.00

NMR ($CDCl_3$) δ: 1.58(9H,s),2.03(3H,s),3.91(3H,s), 3.88-3.98(1H,m),3.98-4.08(2H,m),4.21(1H,dd,J=4Hz, J=10Hz), 4.28(1H,m),5.22(2H,s),7.39-7.49(5H,m),7.95(1H,br,s), 9.17(1H,s)

(EXAMPLE 3)

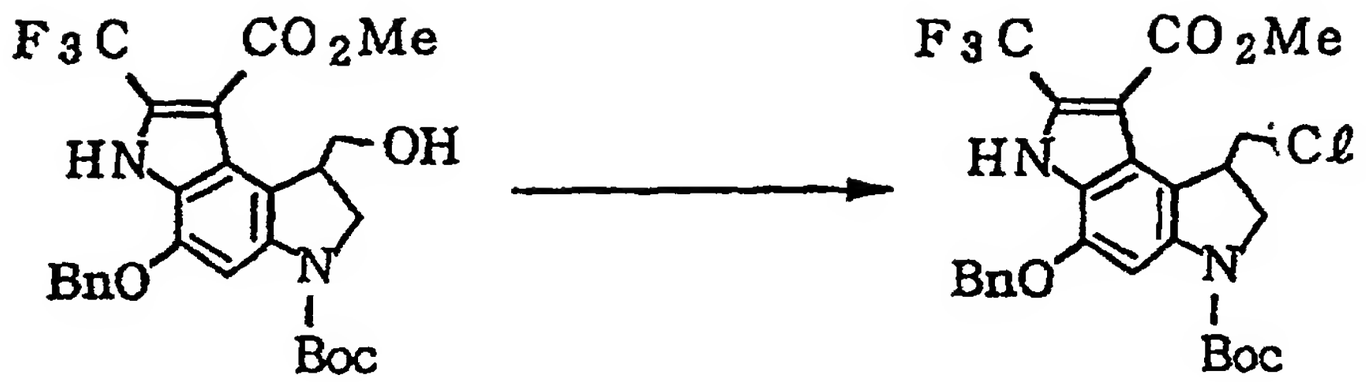
[0025]



[0026] In 4 ml of methanol, was suspended 225 mg (0.4 mmol) of methyl 1-acetoxymethyl-5-benzyloxy-3-t-butoxycarbonyl-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate. Thereto 110.6 mg (0.8 mmol) of potassium carbonate was added, and the mixture was stirred for 7 hours. It was neutralized with 10% citric acid, and diluted with water. The precipitated crystalline matter was collected by filtration, washed with water, and dried. Thereby, methyl 5-benzyloxy-3-t-butoxycarbonyl-1-hydroxymethyl-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared in a colorless crystalline state in a yield of 206.5 mg (99 %).

(EXAMPLE 4)

[0027]



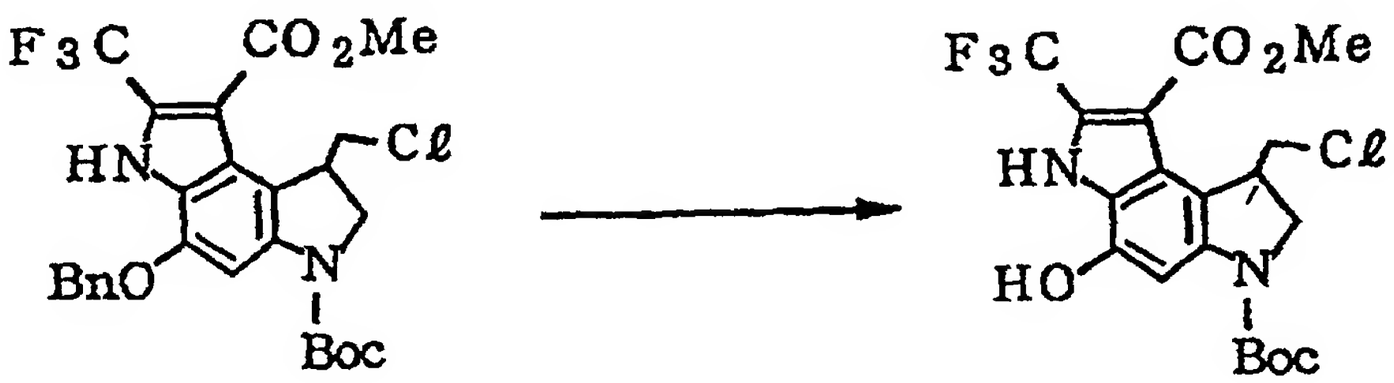
[0028] 104.1 Milligrams (0.2 mmol) of methyl 5-benzyloxy-3-t-butoxycarbonyl-1-hydroxymethyl-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate, and 104.9 mg (0.4 mmol) of triphenylphosphine were suspended in 1 ml of anhydrous acetonitrile. Thereto 115.3 μl (1.2 mmol) of carbon tetrachloride was added dropwise. The mixture was stirred for 5 hours under atmosphere of argon. After removal of the solvent, the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 4 : 1) to obtain methyl 5-ben-zyloxy-3-t-butoxycarbonyl-1-chlorome-thyl-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in a yield of 106.7 mg (99 %).
m.p.161.5～162.5°C

Analysis: $C_{26}H_{26}ClF_3N_2O_5$			
	C	H	N
Calculated	57.94	4.86	5.20
Found	58.17	4.85	5.27

NMR ($CDCl_3$) δ: 1.59(9H,s),3.34(1H,t,J=10.3Hz), 3.82(1H,dd,J=3Hz,J=10Hz),3.96(3H,s),4.01(1H,dd,J=10Hz, J=12Hz),4.21-4.31(2H,m),5.22(2H,s),7.40-7.48(5H,m), 7.95(1H,br,s),9.22(1H,s)

(EXAMPLE 5)

[0029]

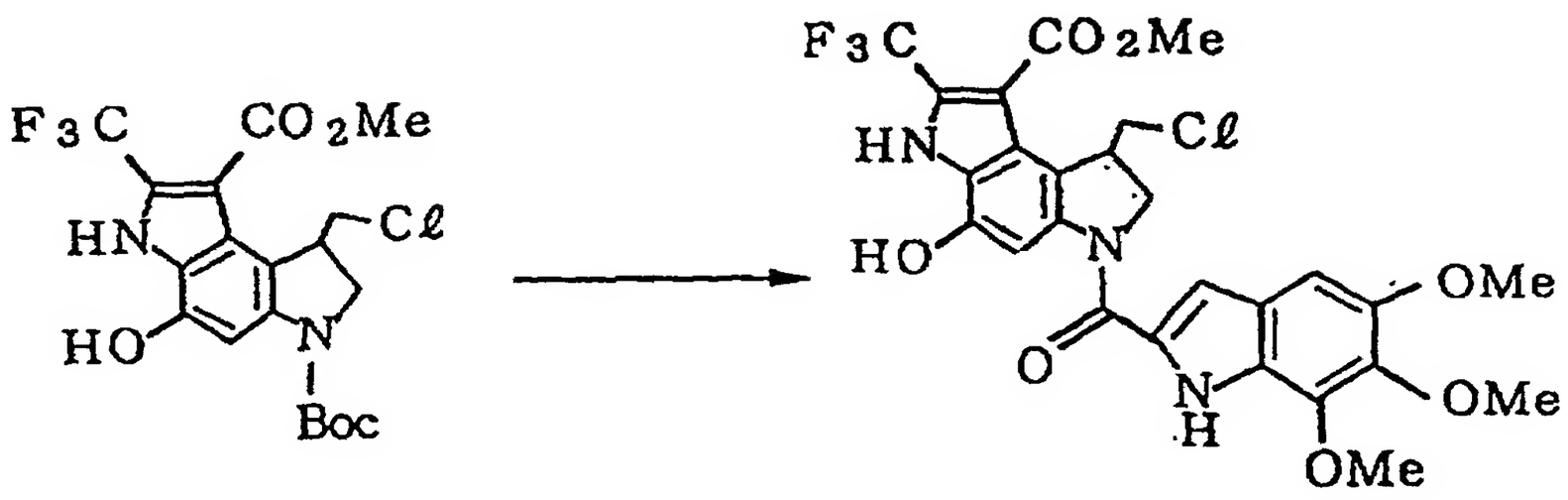


[0030] In 2.63 ml of tetrahydrofuran, was dissolved 106.7 mg (198 μmol) of methyl 5-benzyloxy-3-t-butoxycarbonyl-1-chloromethyl-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate. Thereto, 64 mg of 10% palladium on carbon was added, and then 656.4 μl of 25% ammonium formate was added dropwise under ice cooling. The mixture was stirred for one hour, and then the reaction mixture was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, and the solvent was distilled off to obtain methyl 3-t-butoxycarbonyl-1-chloromethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in a yield of 87.9 mg (99 %).

NMR ($CDCl_3$) δ: 1.59(9H,s),3.33(1H, t, J=10.3Hz), 3.82(1H, dd, J=3Hz, J=10Hz),3.96(3H, s),4.01(1H, dd, J=9Hz, J=12Hz),4.21(1H, d, J=12Hz),4.29(1H, m),7.34(1H, br, s), 7.76(1H, br, s),9.26(1H, s)

(EXAMPLE 6)

[0031]

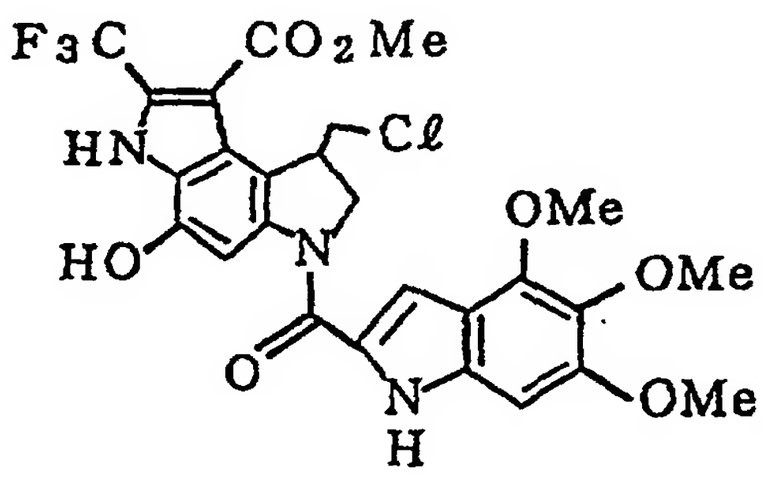


[0032] To 42.6 mg (95 μmol) of methyl 3-t-butoxycarbonyl-1-chloromethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate, 1.6 ml of 3M hydrogen chloride-ethyl acetate was added, and the mixture was stirred at room temperature for one hour. Then the solvent was distilled off. The residue with 23.8 mg (95 μmol) of 5,6,7-trimethoxyindole-2-carboxylic acid, and 54.6 mg (285 μmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride was stirred in 0.95 ml of anhydrous dimethylformamide at room temperature under atmosphere of argon overnight. Water was added to the liquid reaction mixture. The resulting mixture was extracted with methylene chloride, and the extract solution was washed with water, 10% sodium hydrogencarbonate, and saturated sodium chloride solution successively, and dried over anhydrous sodium sulfate. Therefrom the solvent was distilled off. The residue was purified by silica gel column chromatography (chloroform : methanol = 20 : 1) to obtain methyl 1-chloromethyl-5-hydroxy-7-trifluoromethyl-3- (5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in a yield of 45.3 mg (82 %).

NMR ($CDCl_3$) δ: 3.22(1H,t,J=10Hz), 3.76(1H,dd,J=3Hz,J=11Hz),3.80(3H,s),3.82(3H,s),3.85(3H,s), 3.97(3H,s), 4.31(1H,m),4.41(1H,t,J=9Hz),4.60(1H,d,J=10Hz), 6.78(1H,s),6.87(1H,d,J=2Hz),7.89(1H,s),9.15(1H,br,s), 9.45(1H,s)

(EXAMPLE 7)

[0033]

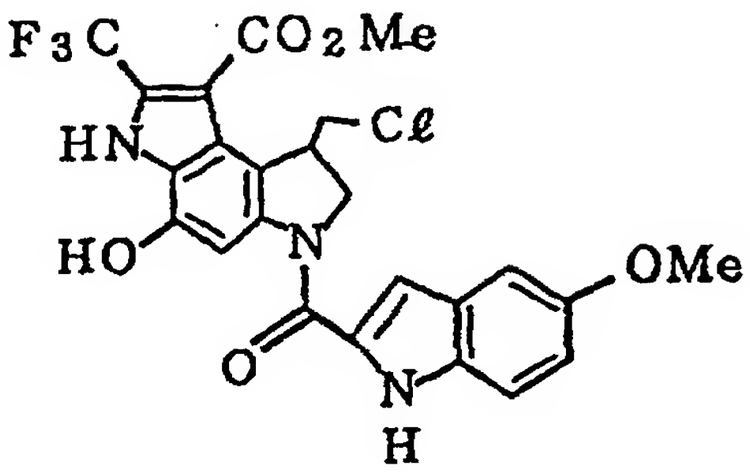


[0034] Methyl 1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-(4,5,6-trimethoxy-1H-indol-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared in the same manner as above by using 5.8 mg (23 μmol) of 4,5,6-trimethoxyindole-2-carboxylic acid in a yield of 10.3 mg (77 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.35(1H,t,J=11Hz),3.86-3.89(1H,m),3.88(3H,s),3.89(3H,s),3.98(3H,s),4.15(3H,s), 4.44(1H,m),4.56(1H,t,J=10Hz),4.74(1H,d,J=10Hz),6.68(1H,s), 7.09(1H,s),8.04(1H,br,s),9.08(1H,s),9.85(1H,s), 11.4 (1H,br,s)

(EXAMPLE 8)

[0035]

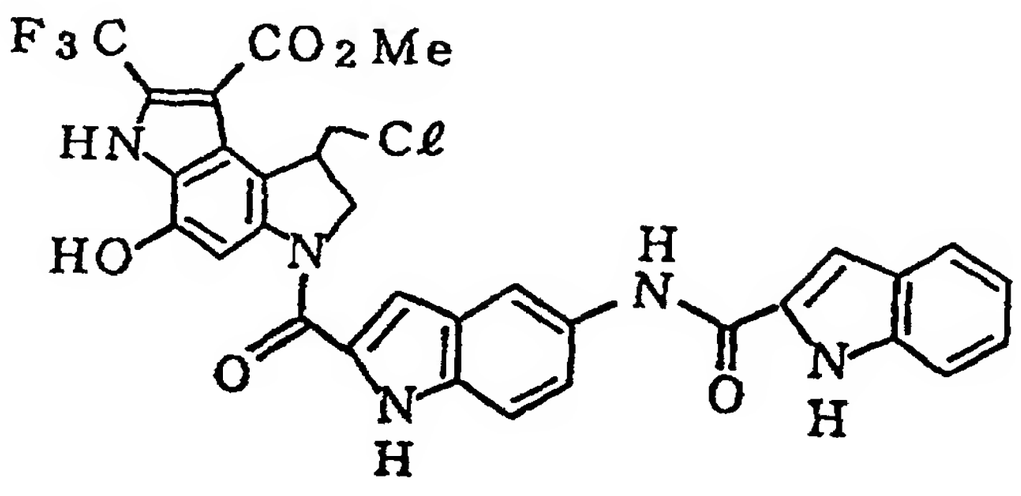


[0036] Methyl 1-chloromethyl-5-hydroxy-3-(5-methoxy-1H-indol-2-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared in the same manner as above by using 11.2 mg (25 μmol) of methyl 3-t-butoxycarbonyl-1-chloromethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate and 4.8 mg (25 μmol) of 5-methoxyindole-2-carboxylic acid in a yield of 7.2 mg (55 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.34(1H, t, J=10Hz), 3.87(3H, s), 3.87-3.91(1H,m),3.97(3H,s), 4.44(1H, m), 4.55(1H, t, J=10Hz), 4,76(1H, d, J=11Hz),6.97-7.01(2H, m),7.13(1H, s), 7.39(1H, d, J=10Hz),8.02(1H, s),9.14(1H, dr, s), 9.81 (1H, br, s),11.45(1H, s)

(EXAMPLE 9)

[0037]

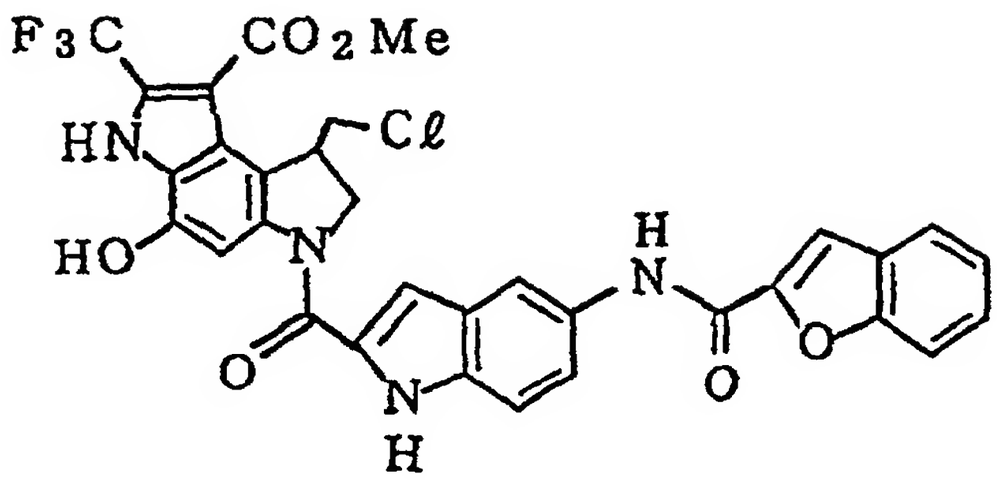


[0038] Methyl 1-chloromethyl-5-hydroxy-3-[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared in the same manner as above by reaction with 8.0 mg (25 μmol) of 5-(lH-indol-2-ylcarbonyl)amino-1H-indole-2-carboxylic acid in a yield of 7.5 mg (46%).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.37(1H,t,J=10Hz), 3.89(1H,dd,J=3Hz,J=10.3Hz),3.96(3H,s),4.40(1H,m), 4.58(1H, t,J=11Hz),4,72(1H,d,J=11Hz),7.04(1H,d,J=2.0Hz), 7.10(1H,t,J=7Hz),7.24(1H,t,J=7Hz),7.36(1H,s),7.50(1H,s), 7.52 (1H,s),7.58(1H,dd,J=2Hz,J=11Hz),7.59-7.63(1H,m) 7.66(1H,d,J=8Hz),7.96(1H,br,s),8.24(1H,s),9.59(1H,br,s), 9.75 (1H,br,s)

(EXAMPLE 10)

[0039]

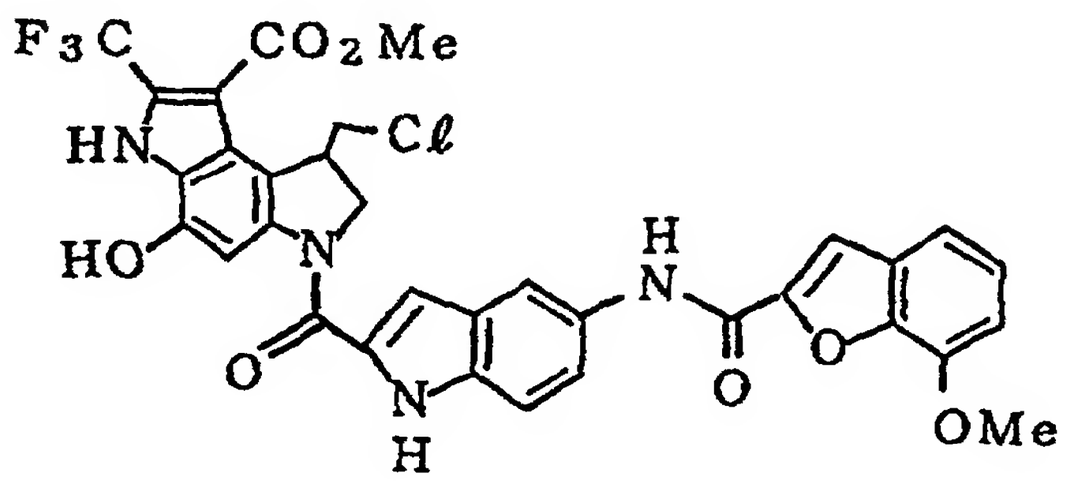


[0040] Methyl 3-[5-[(benzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1-chloromethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared in the same manner as above by using 8.0 mg (25 μmol) of 5-(benzofuran-2-ylcarbonyl)amino-1H-indole-2-carboxylic acid in a yield of 9.1 mg (56 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.37(1H,t,J=10Hz),3.88(1H,m), 3.96(3H,s),4.39(1H,m),4.57(1H,t,J=10Hz),4,71(1H, d,J=11Hz), 7.05(1H,s),7.33(1H,t,J=8Hz),7.46(1H,t,J=8Hz), 7.53(1H,d,J=9Hz),7.58(1H,d,J=9Hz),7.61-7.63(2H,m), 7.73(1H,d,J=8Hz),7.95(1H,br,s),8.22(1H,s),9.57-9.60(2H,m), 11.05(1H,br),12.09(1H,br)

(EXAMPLE 11)

[0041]

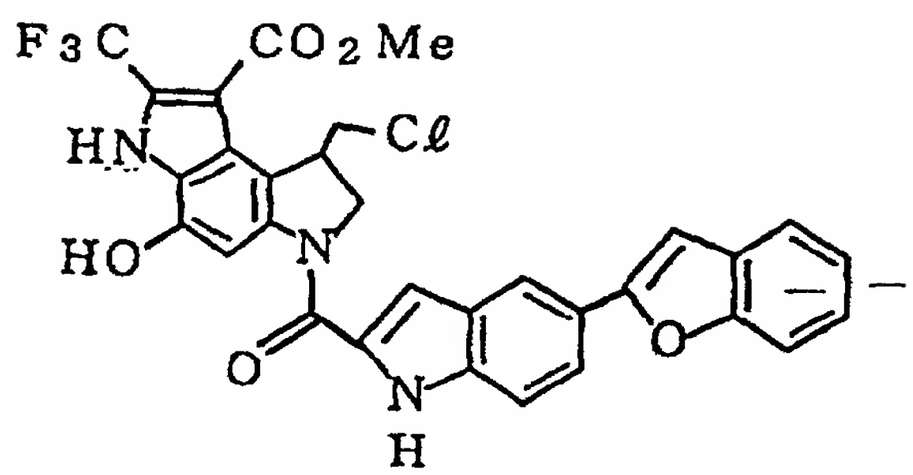


[0042] Methyl 1-chloromethyl-5-hydroxy-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared, in the same manner as above, by using 8.1 mg (23 μmol) of 5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indole-2-carboxylic acid, in a yield of 11.0 mg (70 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.36(1H,t,J=10Hz), 3.89(1H,dd,J=3Hz,J=11Hz),3.98(3H,s),4.07(3H,s),4.45(1H,m), 4.58(1H,t,J=10Hz),4.77(1H,d,J=11Hz),6.96(1H,d,J=8Hz), 7.09(1H,s),7.25(1H,d,J=8Hz),7.28-7.30(1H,m), 7.49(1H,d, J=9Hz),7.53(1H,dd,J=2Hz,J=9Hz),7.60(1H,s), 8.02(1H,br,s),8.22(1H,s),8.65(1H,s),9.13(1H,s),9.93(1H,s), 11.39(1H, br)

(EXAMPLE 12)

[0043]

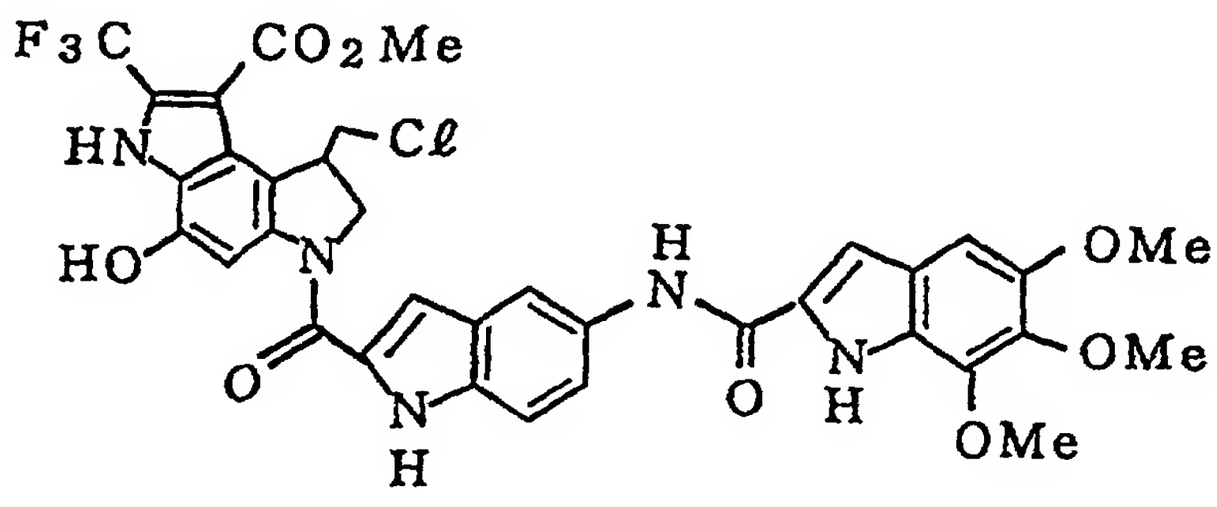


[0044] Methyl 3-(5-benzofuran-2-yl)-1H-indol-2-yl-carbon-yl)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 6.4 mg (23μmol) of 5-(benzofuran-2-yl)-1H-indole-2-carboxylic acid, in the same manner as above, in a yield of 10.6 mg (76 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.37(1H,t,J=10Hz), 3.90(1H,dd,J=3Hz,J=10Hz),3.98(3H,s),4.47(1H,m), 4.59(1H,t, J=10.3Hz),4.78(1H,d,J=11Hz),7.00(1H,s), 7.14(1H,s),7.21-7.29(2H,m),7.52-7.59(3H,m), 7.81(1H,d,d,J=2Hz,J=9Hz), 8.02(1H,br),8.27(1H,s),9.17(1H,s), 10.3(1H,s),11.5(1H,br)

(EXAMPLE 13)

[0045]

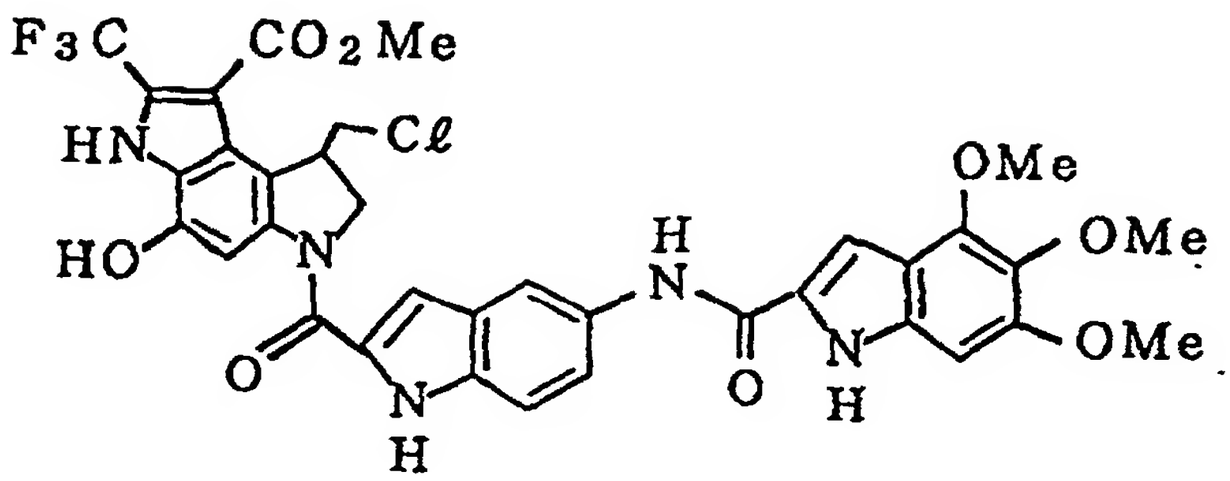


[0046] Methyl 1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-[5-[(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 9.4 mg (23 μmol) of 5-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)amino-1H-indole-2-carboxylic acid, in the same manner as above, in a yield of 13.2 mg (78%).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.36(1H,t,J=10Hz),3.89(1H,m), 3.92(3H,s),3.95(3H,s),3.98(3H,s),4.10(3H,s),4.45 (1H,m), 4.57(1H,t,J=10Hz),4.77(1H,d,J=10Hz),6.86(1H,s),7.06(1H,s), 7.17(1H,s),7.47(1H,d,J=9Hz),7.53(1H,dd, J=2Hz,J=9Hz), 8.02(1H,s),8.20(1H,s),9.07(1H,s),9.11(1H,s), 9.87(1H,s),9.91(1H,s),11.39(1H,s)

(EXAMPLE 14)

[0047]

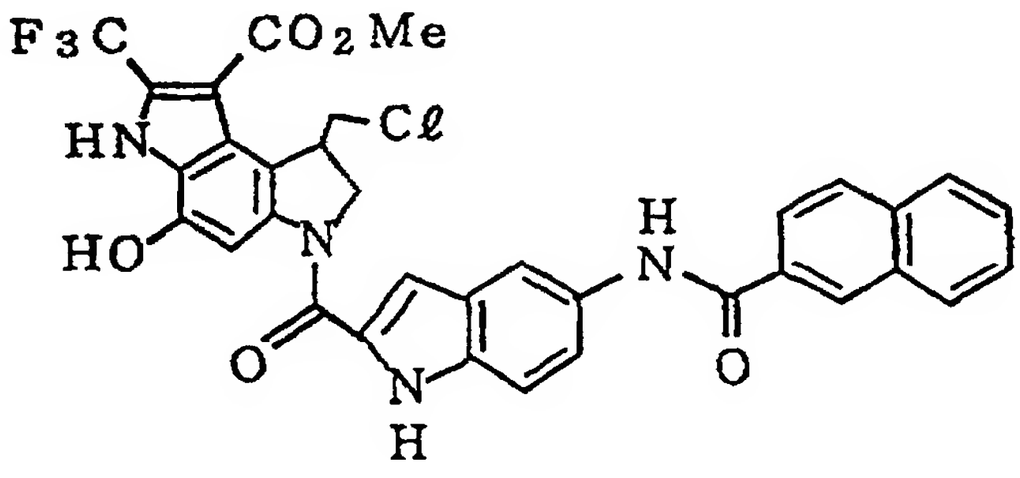


[0048] Methyl 1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-[5-[(4,5,6-trimethoxy-1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 9.4 mg (23 μmol) of 5-(4,5,6-trimethoxy-1H-indol-2-ylcarbonyl)amino-1H-indole-2-carboxylic acid, in the same manner as above, in a yield of 8.5 mg (50 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.36(1H, t, J=10Hz), 3.81-3.93(1H, m), 3.877 (3H, s),3.879(3H,s), 3.98(3H,s), 4.15 (3H,s), 4.45(1H, m),4.57(1H, t, J=10Hz),4.77(1H, d, J=10Hz),6.68(1H,s), 7.06(1H,s),7.35(1H,s),7.47(1H,d,J=9Hz), 7.54(1H,d,J=9Hz), 8.03(1H,s),8.21(1H,s),8.99(1H,s),9.15(1H,s),10.02(1H,s), 10.09(1H,s),11.44(1H,br)

(EXAMPLE 15)

[0049]

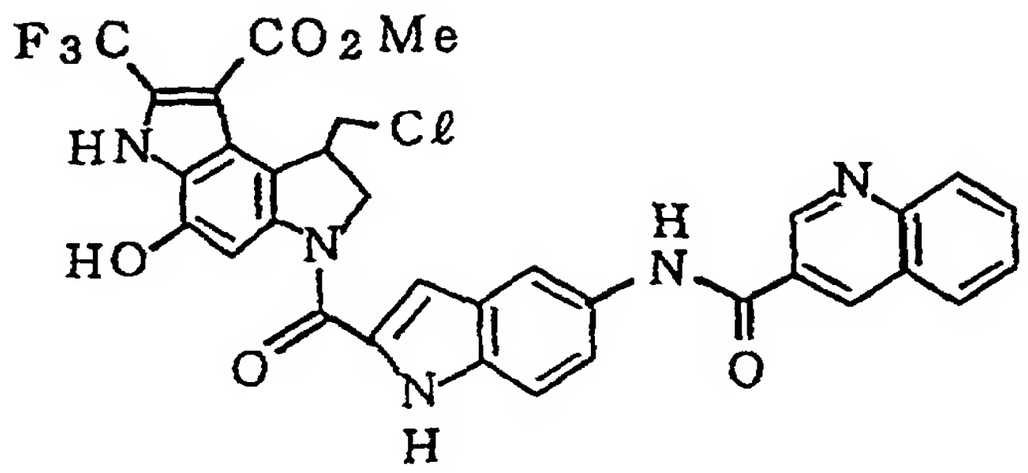


[0050] Methyl 1-chloromethyl-5-hydroxy-3-[5-[(naphthalene-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared in the same manner, by using 6.3 mg (19 μmol) of 5-(naphthalene-3-ylcarbonyl)amino-1H-indol-2-carboxylic acid, in a yield of 10.1 mg (80 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.37(1H,t,J=10Hz), 3.89(1H,dd,J=3Hz,J=11Hz),3.98(3H,s),4.44(1H,m), 4.57(1H,t, J=9Hz),4.76(1H,d,J=11Hz),7.07(1H,s), 7.50(1H,d,J=9Hz),7.55-7.61(3H,m),7.90-8.00(h,m), 8.07(1H,d,J=9Hz),8.25 (1H,s),8.54(1H,s),9.24(1H,s), 9.36(1H,s),10.22(1H,s),11.60(1H,br)

(EXAMPLE 16)

[0051]

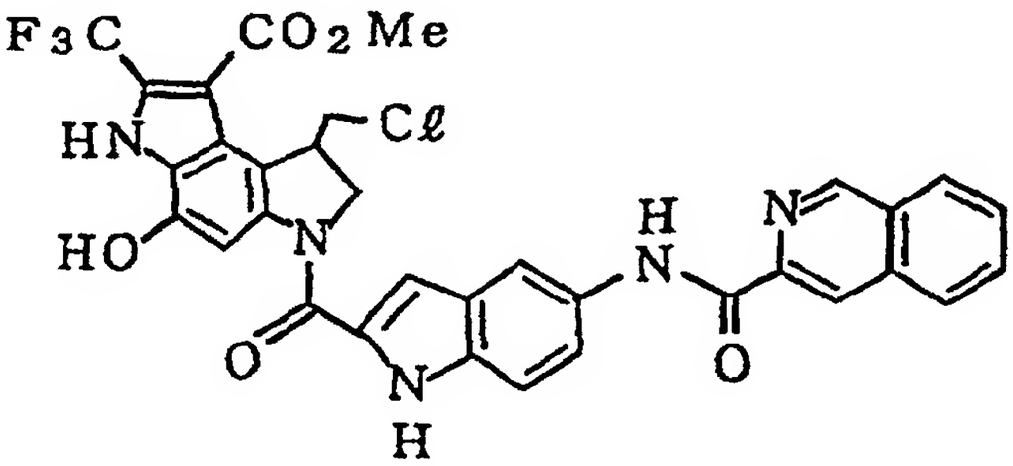


[0052] Methyl 1-chloromethyl-5-hydroxy-3-[5-[(quinoline-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared in the same manner, by using 7.6 mg (23 μmol) of 5-(quinoline-3-ylcarbonyl)amino-1H-indole-2-carboxylic acid, in a yield of 6.4 mg (42 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.37(1H, t, J=10Hz), 3.89(1H, dd, J=3Hz, J=11Hz),3.98(3H, s),4.44(1H, m), 4.58(1H, t, J=10Hz),4.77(1H, d, J=11Hz),7.07(1H, s), 7.49(1H, d, J=9Hz),7.61(1H, d, J=10Hz), 7.66(1H, d, J=7Hz), 7.83(1H,t, J=7Hz),7.97-8.01(1H,m),8.18(1H,d,J=8Hz), 8.25(1H,s),8.87(1H,s),9.23(1H,s),9.53(1H,s),9.77(1H,br), 10.12(1H,br), 10.79(1H,br),11.51(1H,br)

(EXAMPLE 17)

[0053]

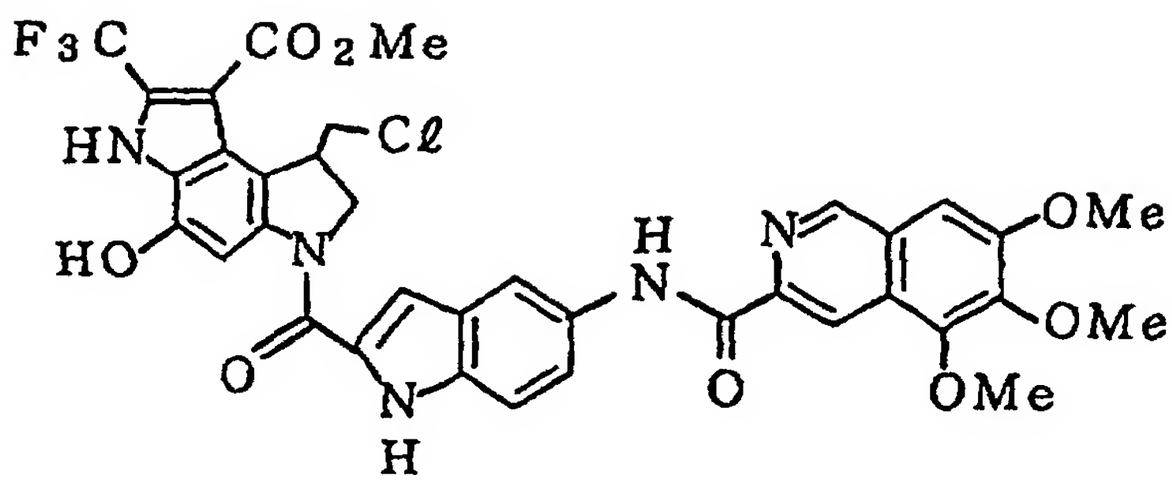


[0054] Methyl 1-chloromethyl-5-hydroxy-3-[5-[(isoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 7.6 mg (23 μmol) of 3-(5-isoquinolin-3-ylcarbonyl)amino-1H-indole-2-carboxylic acid, in the same manner as above, in a yield of 8.3 mg (54 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.37(1H, t, J=8Hz),3.87-3.98(1H, m),3.98(3H, s),4.44(1H, m),4.58(1H, t, J=8Hz), 4.77(1H, d, J=11Hz),7.09(1H, s),7.53(1H, d, J=9Hz), 7.60(1H, d, J=9Hz),7.75(1H, t, J=8Hz),7.82(1H, t, J=8Hz), 8.01-8.06(2H,m),8.10(1H, d, J=8Hz),8.39(1H,s),8.74(1H,s), 9.22(1H, br, s),9.26(1H, s),10.19(1H, br, s),10.31(1H, s), 11.56(1H, br, s)

(EXAMPLE 18)

[0055]

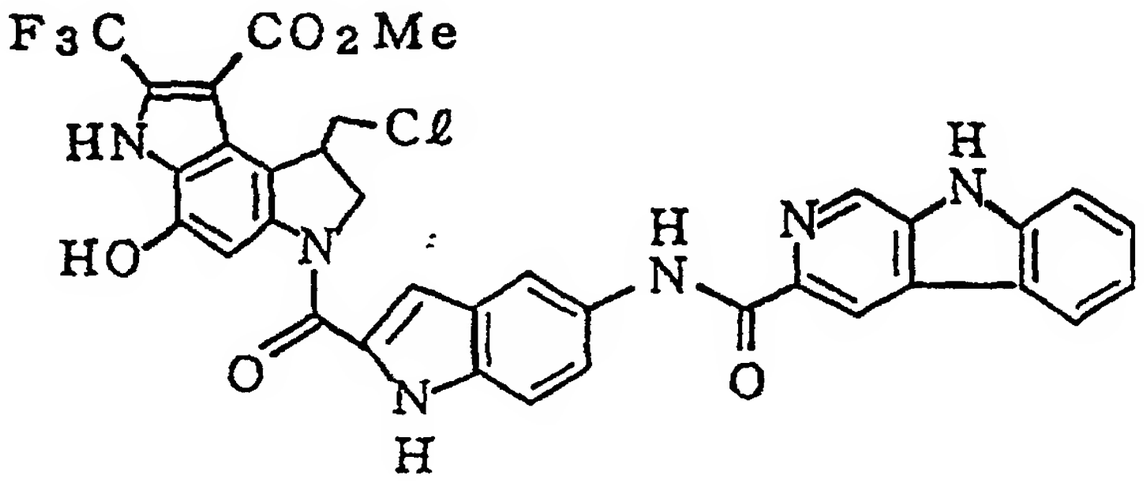


[0056] Methyl 1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-[5-[(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 9.7 mg (23 μmol) of 5-(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)amino-1H-indole-2-carboxylic acid, in the same manner as above, in a yield of 15.4 mg (89 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.37(1H,t,J=10Hz),3.89(1H,m), 3.98(3H,s),4.05(3H,s),4.07(3H,s),4.12(3H,s),4.44(1H, m), 4.58(1H,m),4.77(1H,d,J=7Hz),7.08(1H,s),7.17(1H,s), 7.52(1H,d,J=7Hz),7.60(1H,m),8.00(1H,br,s),8.37(1H,s), 8.87 (1H,s),9.06(1H,s),9.23(1H,s),10.25(1H,br),10.92(1H,br), 11.58(1H,br)

(EXAMPLE 19)

[0057]

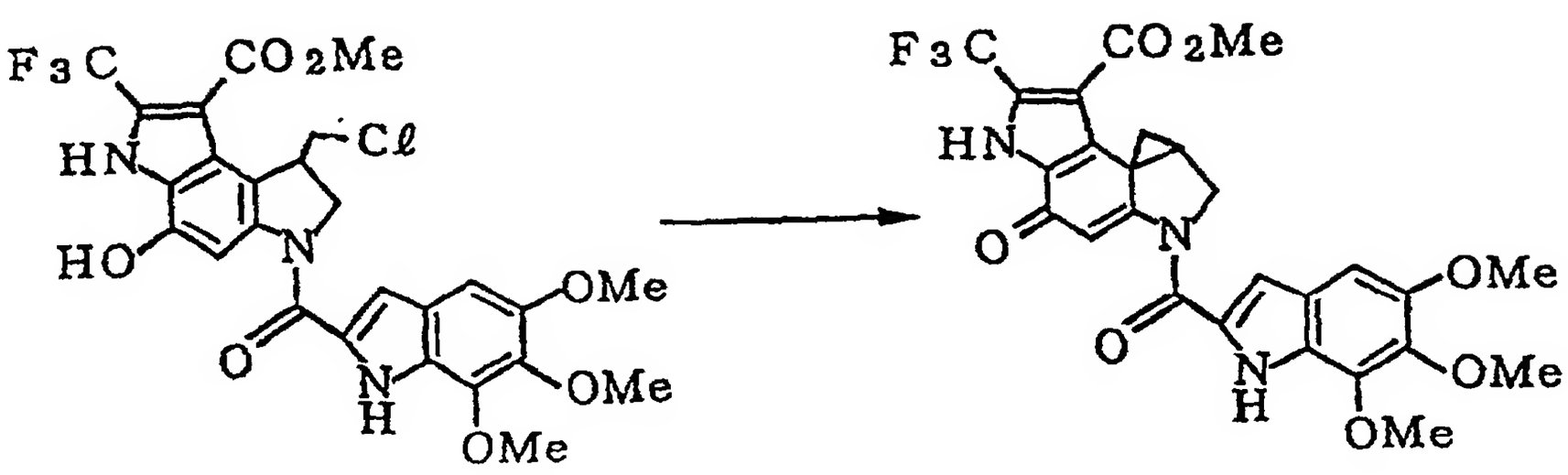


[0058] Methyl 1-chloromethyl-5-hydroxy-3-[5-[(9H-pyrido[3,4-b]indol-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 8.5 mg (23 μmol) of 5-(9H-pyrido[3,4-b]indol-3-ylcarbonyl)amino-1H-indole-2-carboxylic acid, in the same manner as above, in a yield of 12.5 mg (78 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.37(1H, t, J=10Hz), 3.90(1H,d,J=11Hz),3.98(3H,s),4.44(1H,m),4.59(1H,t,J=10Hz), 4.77(1H,d,J=11Hz),7.09(1H,s),7.33(1H,t,J=8Hz), 7.53(1H,d,J=9Hz),7.57-7.62(3H,m),8.01(1H,br,s), 8.24(1H,d,J= 8Hz),8.37(1H,s),8.89(1H,s),9.01(1H,s), 9.27(1H,s),10.25(2H,m),11.03(1H,s),11.63(1H,br)

(EXAMPLE 20)

[0059]

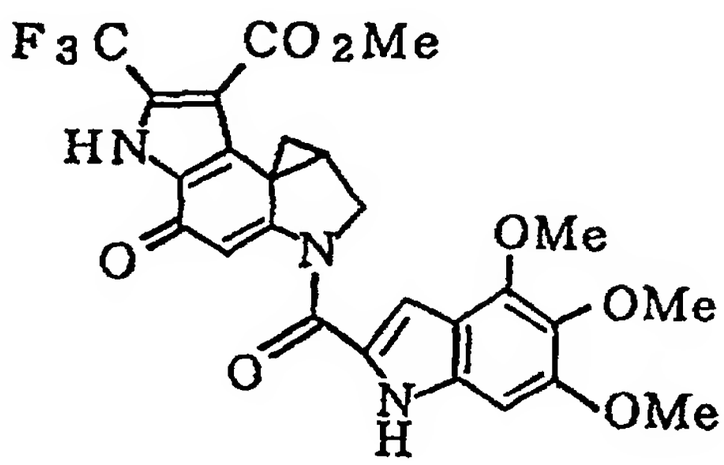


[0060] In 2.2 ml of acetonitrile, was suspended 8.0 mg (14 μmol) of methyl 1-chloromethyl-5-hydroxy-7-trifluorome-thyl-3-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate. Thereto 4 μl of 1,8-diazabicyclo[5.4.0]-7-undecene was added, and the mixture was stirred under atmosphere of argon for 3 hours. Then 0.5M phosphate buffer solution was added thereto, and the mixture was extracted with ethyl acetate. The extract was washed with water, and saturated sodium chloride solution successively, and was dried over anhydrous sodium sulfate. The solvent was removed by distillation, and the residue was purified by silica gel column chromatography (methylene chloride : ethyl acetate = 1 : 1). Thereby, methyl 6-trifluoromethyl-2-(5,6,7-trimethoxy-1H-indol-2-ylcarbo-nyl)-1,2,8,8a-tetrahydrocyclopropa[c]-pyrrolo[3,2-e]indole-4(5H)-one-7-carboxylate was prepared in a pale yellow crystalline state in a yield of 6.6 mg (89 %).

NMR ($CDCl_3$) δ: 1.42(1H,t,J=4Hz), 2.38(1H,dd,J=4Hz,J=8Hz),3.68(1H,m),3.87(3H,s),3.89(3H,s), 3.94(3H,s), 4.07(3H,s),4.46(2H,m),6.80(1H,s), 6,95(1H,d,J=2Hz),7.15(1H,s),9.41(1H,s)

(Example 21)

[0061]

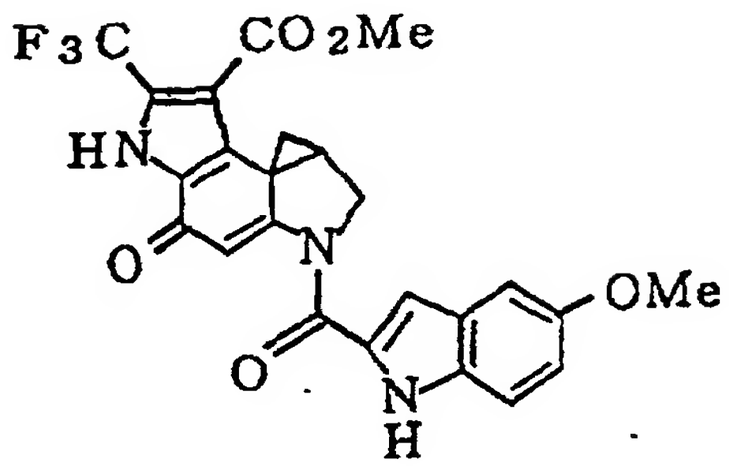


[0062] Methyl 6-trifluoromethyl-2-(4,5,6-trimethoxy-1H-indol-2-ylcarbonyl)-1,2,8,8a-tetrahydrocyclopropa[c]-pyrrolo [3,2-e]indol-4(5H)-one-7-carboxylate was prepared in the same manner as above by using 7.4 mg (13 μmol) of methyl 1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-(4,5,6-trimethoxy-1H-indol-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo [3,2-e]indole-8-carboxylate in a yield of 6.7 mg (97 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 1.39(1H,t,J=4Hz), 2.33(1H,dd,J=3Hz,J=8Hz),3.65(1H,m),3.87(6H,s),3.92(3H,s), 4.11(3H, s),4.49(2H, m),6.66(1H, s),7.05(1H, s),7.17(1H, s), 10.03(1H, s),11.80(1H, br)

(EXAMPLE 22)

[0063]

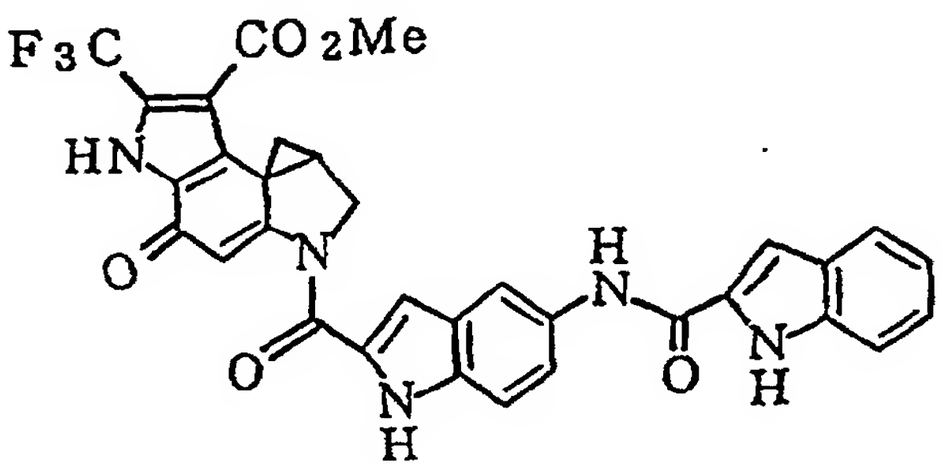


[0064] Methyl 2-(5-methoxy-1H-indol-2-ylcarbonyl)-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]-pyrrolo [3,2-e]indole-4(5H)-one-7-carboxylate was prepared in the same manner as above by using 5.6 mg (11 μmol) of methyl 1-chloromethyl-5-hydroxy-3-(5-methoxy-1H-indol-2-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in a yield of 4.3 mg (82 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 1.42(1H,t,J=4Hz), 2.31(1H,dd,J=4Hz,J=8Hz),3.62(1H,m),3.84(3H,s),3.86(3H,s), 4.46(1H, d, J=10Hz),4. 50(1H, dd, J=4Hz, J=10Hz),6.94-6.96(2H, m), 7.04(2H, s),7.41(1H, d, J=9Hz)

(EXAMPLE 23)

[0065]

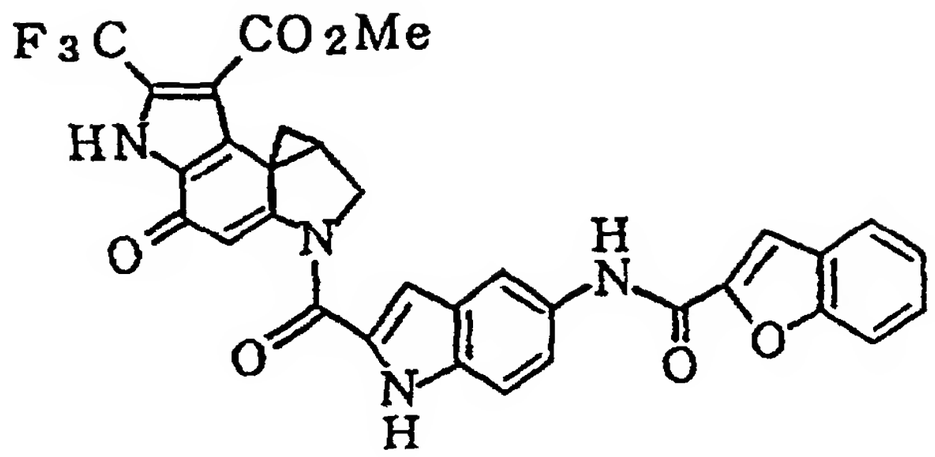


[0066] Methyl 2-[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indole-4(5H)-one-7-carboxylate was prepared by using 6.0 mg (9 μmol) of methyl 1-chloromethyl-5-hydroxy-3-[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo [3,2-e]indole-8-carboxylate in the same manner as above in a yield of 5.5 mg (96 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 1.43(1H,t,J=4Hz), 2.32(1H,dd,J=3Hz,J=7Hz),3.62(1H,m),3.86(3H,s), 4.48(1H,d, J=10Hz),4.54(1H,dd,J=4Hz,J=10Hz),7.03(1H,s), 7.05(1H,s),7.10(1H,t,J=7Hz),7.24(1H,t,J=7Hz),7.35(1H,s), 7.50(1H, d,J=9Hz),7.51(1H,d,J=7Hz),7.57(1H,d,J=2Hz), 7.66(1H,d,J=8Hz),8.00(1H,s),8,23(1H,s),9.71(1H,s), 10.95(1H,s), 11.30(1H,s)

(EXAMPLE 24)

[0067]

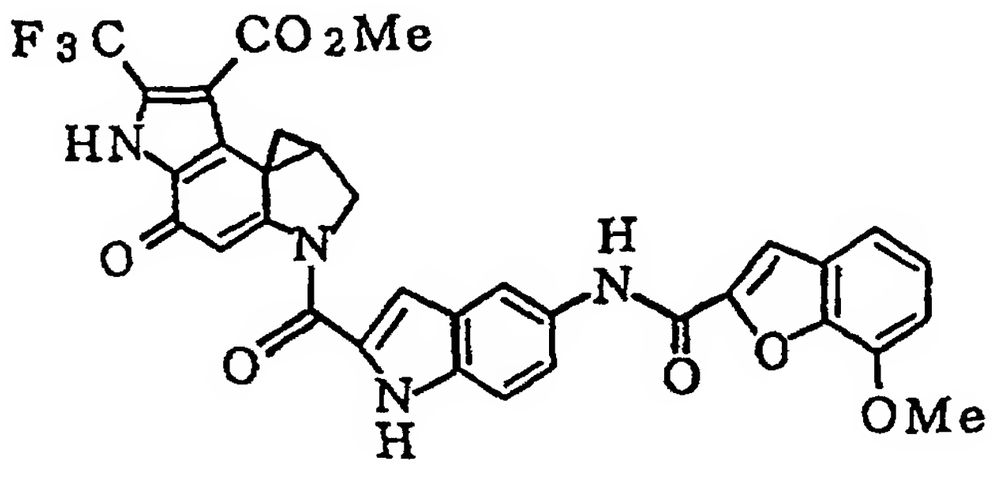


[0068] Methyl 2-[5-[(benzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indole-4(5H)-one-7-carboxylate was prepared by using 7.3 mg (11 μmol) of methyl 3-[5-[(benzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1-chloromethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as above in a yield of 5.9 mg (85 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 1.41(1H,t,J=4Hz), 2.34(1H,dd,J=3Hz,J=8Hz),3.66(1H,m),3.86(3H,s),4.46-4.57(2H,m),7.03(1H,s),7.15(1H,s),7.33(1H,m), 7.46(1H,t,J=7Hz),7.50(2H,s),7.58-7.61(2H,m), 7.72(1H,d,J=8Hz),8.26(1H,s),8.75(1H,s),10.63(1H,s), 12.30(1H,br)

(EXAMPLE 25)

[0069]

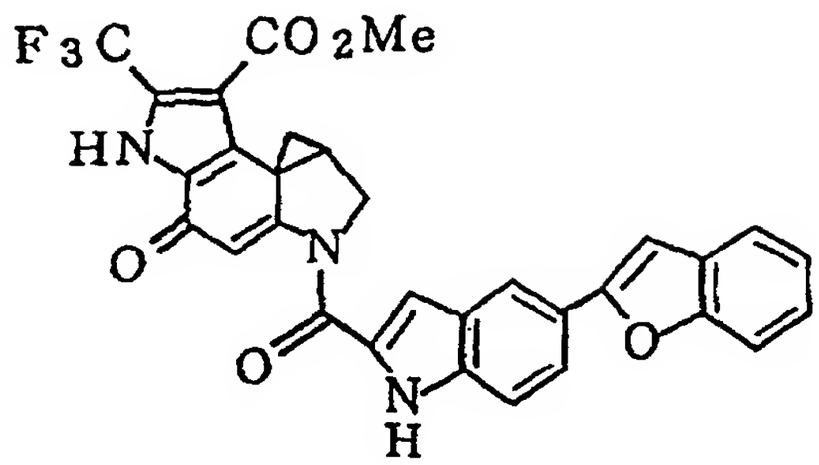


[0070] Methyl 2-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indole-4(5H)-one-7-carboxylate was prepared by using 9.6 mg (14 μmol) of methyl 1-chloromethyl-5-hydroxy-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as above in a yield of 8.5 mg (94 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 1.42(1H,t,J=4Hz), 2.34(1H,dd,J=4Hz,J=8Hz),3.66(1H,m),3.87(3H,s),4.07(3H,s),4.51(2H,m),6.96(1H,d,J=8Hz),7.04(1H,s),7.16(1H,s), 7.26(1H,t,J=7Hz),7.30(1H,d,J=8Hz),7.50(2H,m),7.60(1H,s),8.24(1H,s),8.72(1H,s),10.60(1H,s),12.30(1H,br)

(EXAMPLE 26)

[0071]

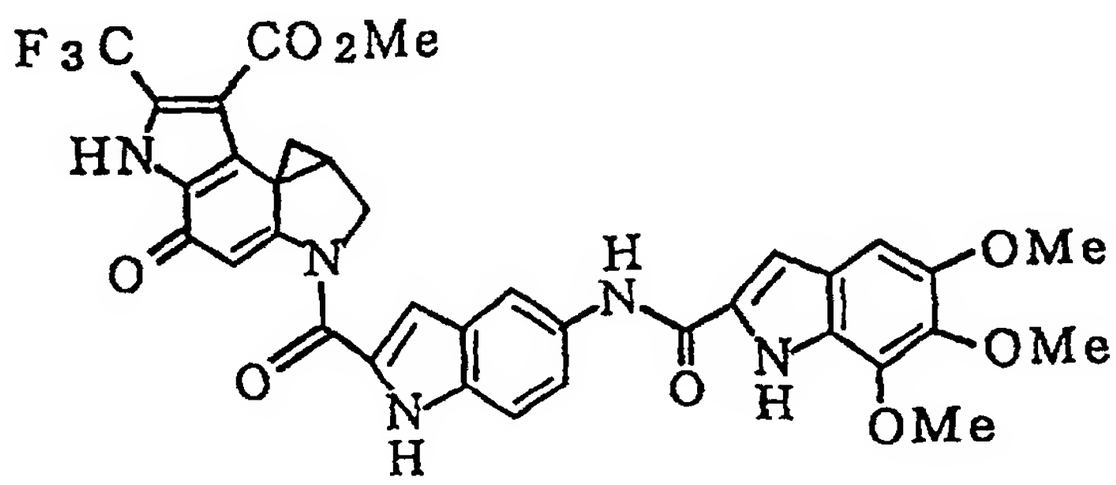


[0072] Methyl 3-(5-(benzofuran-2-yl)-1H-indol-2-ylcarbonyl)-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indole-4(5H)-one-7-carboxylate was prepared by using 8.3 mg (14 μmol) of methyl 3-(5-(benzofuran-2-yl)-1H-indol-2-ylcarbonyl)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as above in a yield of 7.6 mg (98 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 1.43(1H, t, J=4Hz), 2. 35(1H,dd,J=4Hz,J=8Hz),3.66(1H, m),3.87(3H, s),4.51(2H,m), 6.99(1H,s),7.09(1H,s),7.13(1H,s),7.21-7.29(2H,m), 7.52(1H,d,J=7Hz),7.57(1H,s),7.59(1H,s), 7.81(1H,dd,J=2Hz, J=9Hz),8.21(1H,s),10.92(1H,s),12.40(1H,br)

(EXAMPLE 27)

[0073]

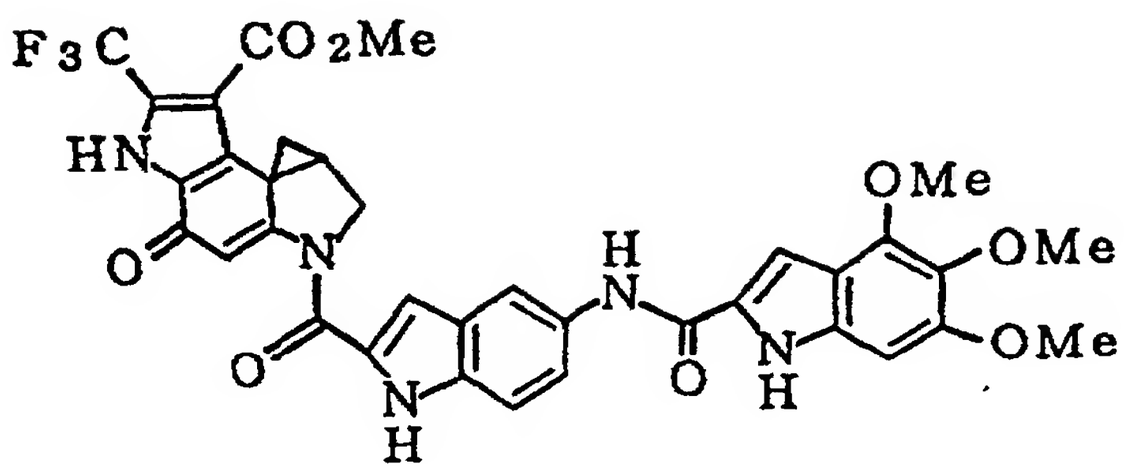


[0074] Methyl 6-trifluoromethyl-2-[5-[(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl]amino]-1H-indol-2-ylcarbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indole-4(5H)-one-7-carboxylate was prepared by using 11.6 mg (16 μmol) of methyl 1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-[5-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as above in a yield of 8.8 mg (79 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 1.42(1H, dd, J=4Hz, J=4Hz), 2.33(1H, dd, J=4Hz, J=8Hz),3.65(1H, m),3.86(3H, s), 3.91(3H, s), 3.94(3H,s),4.10(3H, s),4.49(1H, d, J=10.3Hz), 4.53(1H, dd, J=4Hz, 10Hz),6.86(1H, s),7.02(1H, s),7.11 (1H,s), 7.23(1H, s),7.48(1H, d, J=10Hz),7.53(1H, dd, J=2Hz, 9Hz), 8.25(1H, s),9.49(1H, s),10.23(1H,s),10.85(1H, s), 12.71(1H, br)

(EXAMPLE 28)

[0075]

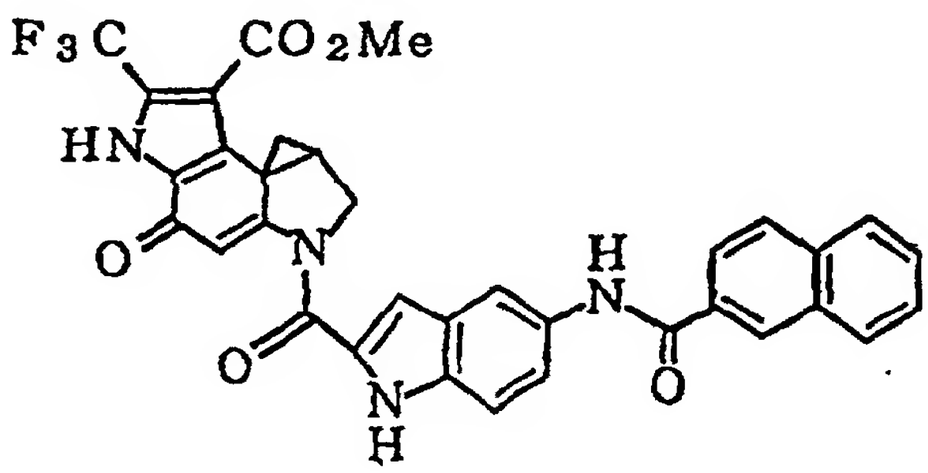


[0076] Methyl 6-trifluoromethyl-2-[5-[(4,5,6-trimethoxy-1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indole-4(5H)-one-7-carboxylate was prepared by using 6.5 mg (8.8 μmol) of methyl 1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-[5-[(4,5,6-trimethoxy-1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as above in a yield of 6.1 mg 98%).

[0077] NMR ($CDCl_3$ + $DMSOd_6$) δ: 1.42(1H,t,J=4Hz), 2.34(1H,dd,J=4Hz,J=8Hz),3.66(1H,m),3.866(3H,s),3.875(3H,s), 3.88(3H,s),4.14(3H,s),4.50(2H,s),6.66(1H,s),7.01(1H,s), 7.16(1H,s),7.33(1H,s),7.45(1H,d,J=8Hz),7.51(1H,d,J=8Hz), 8.22(1H,s),8.93(1H,s),9.97(1H,s),10.32(1H,s),11.86(1H,br)

(EXAMPLE 29)

[0078]

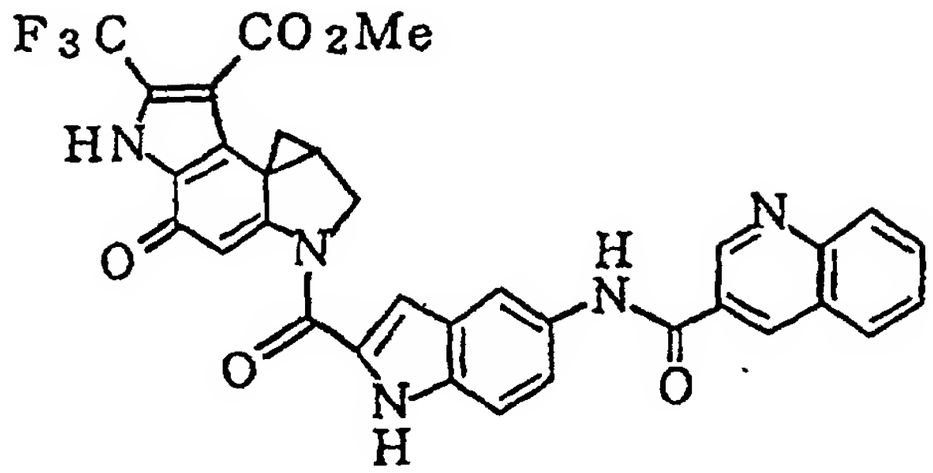


[0079] Methyl 3-[5-[(naphthalene-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate was prepared by using 8.1 mg (12 μmol) of methyl 1-chloromethyl-5-hydroxy-3-[5-[(naphthalene-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as above in a yield of 7.0 mg (92 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 1.42(1H,t,J=4Hz), 2.33(1H,dd,J=4Hz,J=7Hz),3.65(1H,m),3.87(1H,s), 4.51(2H,m), 7.04(1H,m),7.13(1H,s),7.50(1H,d,J=9Hz), 7.57- 7.59(3H,m),7.91(1H,d,J=8Hz),7.95(1H,d,J=9Hz), 7.99(1H,d,J=7Hz), 8.06(1H,d,J=8Hz),8.28(1H,s),8.53(1H,s), 9.38(1H,s),10.72(1H,s),12.60(1H,br)

(EXAMPLE 30)

[0080]

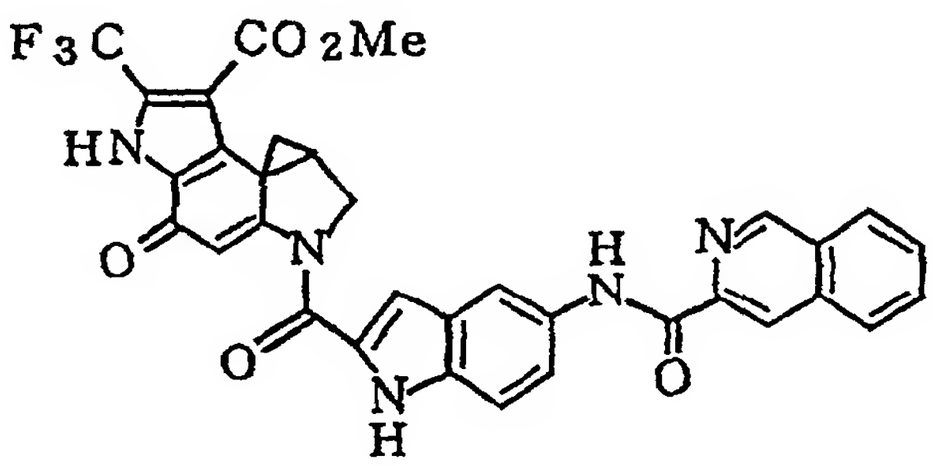


[0081] Methyl 3-[5-[(quinoline-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate was prepared by using 4.7 mg (7.1 μmol) of methyl 1-chloromethyl-5-hydroxy-3-[5-[(quinoline-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tatrahydropyrrolo [3,2-e]indole-8-carboxylate in the same manner as above in a yield of 4.1 mg (93 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 1.44(1H,t,J=4Hz), 2.32(1H,dd,J=4Hz,J=8Hz),3.64(1H,m),3.86(3H,s),4.49-4.60(2H, m),7.06(1H,s),7.53-7.69(3H,m),7.84(1H,t,J=7Hz), 8.00(1H,d,J=8Hz),8.15(1H,d,J=8Hz),8.26(1H,s),8.91(1H,s), 9.50 (1H,s),10.27(1H,s),11.38(1H,s),11.46(1H,s),13.15(1H,br)

(EXAMPLE 31)

[0082]

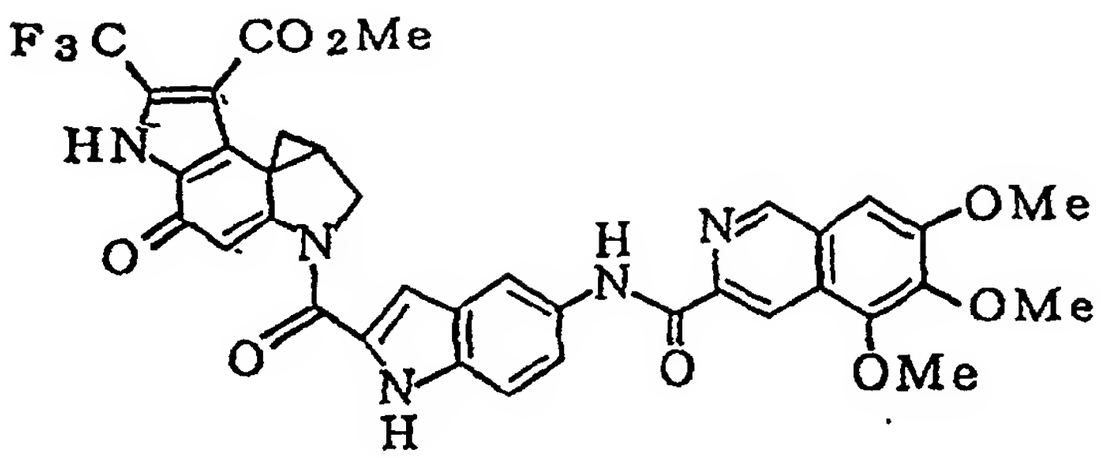


[0083] Methyl 3-[5-[(isoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate was prepared by using 5.3 mg (8 μmol) of methyl 1-chloromethyl-5-hydroxy-3-[5-[(isoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-2,3,6-tetrahydropyrrolo [3,2-e]indole-8-carboxylate in the same manner as above in a yield of 4.9 mg (97 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 1.42(1H,t,J=4Hz), 2.34(1H,dd,J=4Hz,J=8Hz),3.67(1H,m),3.87(3H,s),4.50-4.56(2H, m),7.06(1H,s),7.17(1H,s),7.52(1H,d,J=9Hz), 7.57(1H,dd,J=8Hz),7.75(1H,t,J=7Hz),7.80(1H,t,J=7Hz), 8.05(1H,d, J=8Hz),8.10(1H,d,J=8Hz),8.41(1H,d,J=2Hz), 8.79(1H,s),9.25(1H,s),10.30(1H,s), 10.46(1H,s),12.20(1H,s)

(EXAMPLE 32)

[0084]

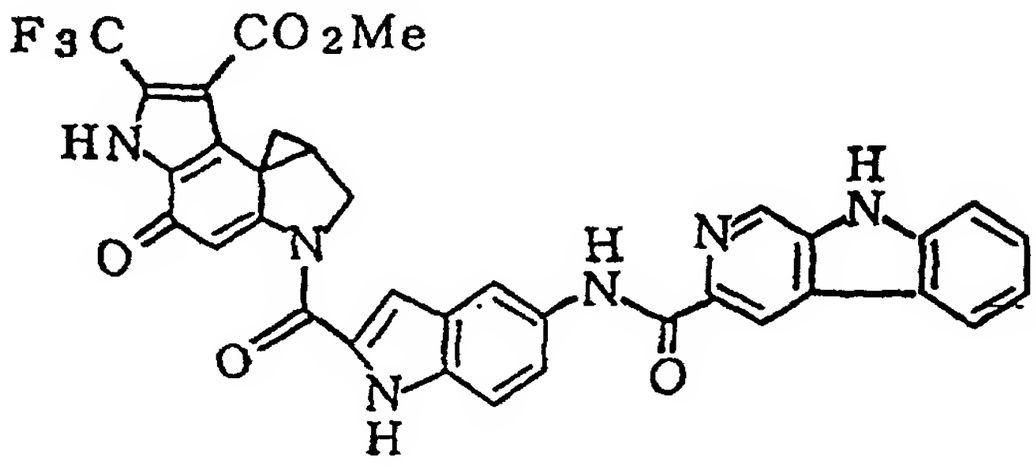


[0085] Methyl 6-trifluoromethyl-2-[5-((5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate was prepared by using 12.8 mg (17 μmol) of methyl 1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-[5-[(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as above in a yield of 11.2 mg (92 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 1.42(1H,t,J=4Hz), 2.32(1H,dd,J=4Hz,J=8Hz),3.65(1H,m),3.86(3H,s),4.05(3H,s), 4.07(3H,s),4.11(3H,s),4.50(1H,d,J=10Hz),4.55(1H,dd,J=4Hz, J=10Hz),7.04(1H,s),7.11(1H,s),7.46(1H,s),7.53(1H,d, J=9Hz), 7.57(1H,dd,J=2Hz,J=9Hz),8.37(1H,s),8.84(1H,s),9.06(1H,s), 10.26(1H,s),11.11(1H,s),12.85(1H,br)

(EXAMPLE 33)

[0086]

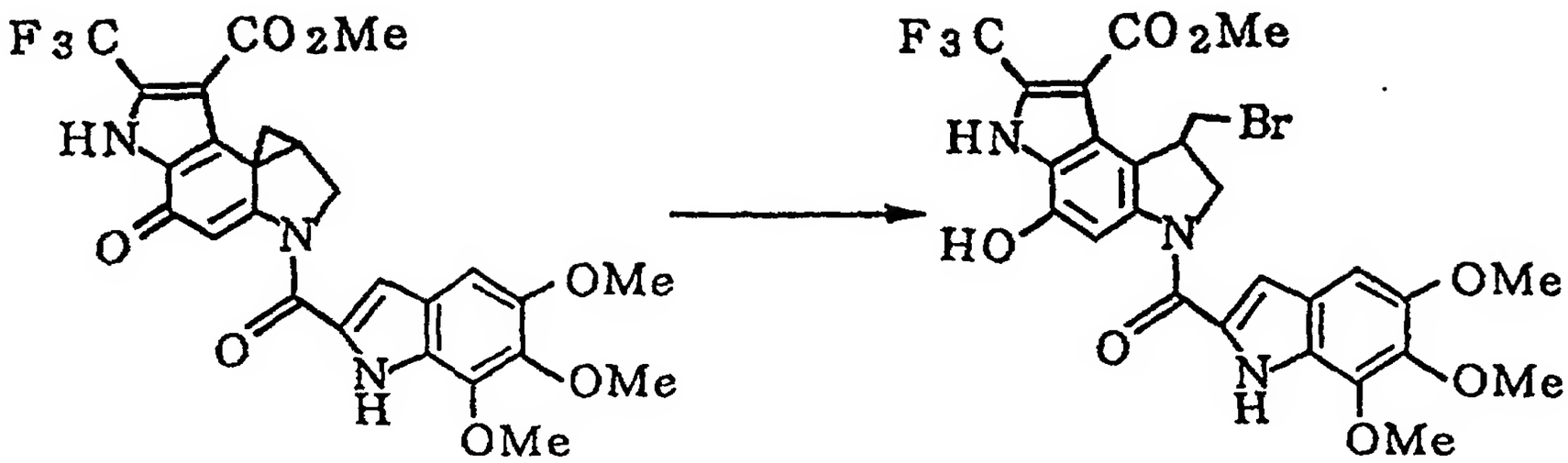


[0087] Methyl 2-[5-[(9H-pyrido[3,4-b]indol-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate was prepared by using 10.2 mg (15 μmol) of methyl 1-chloromethyl-5-hydroxy-3-[5-[(9H-pyrido[3,4-b]indol-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as above in a yield of 8.4 mg (87 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ:1.42(1H,t,J=4Hz), 2.33(1H,dd,J=4Hz,J=7Hz),3.65(1H,m),3.86(3H,s),4.53(2H,m), 7.05(1H,m),7.15(1H, s), 7.33(1H,t,J=8Hz),7.53-8.23(1H,d, J=8Hz), 8.39(1H,s),8.88(1H,s),9.01(1H,s),10.24(1H,s), 10.73(1H,s),11.00(1H,s),12.60(1H,br)

(EXAMPLE 34)

[0088]

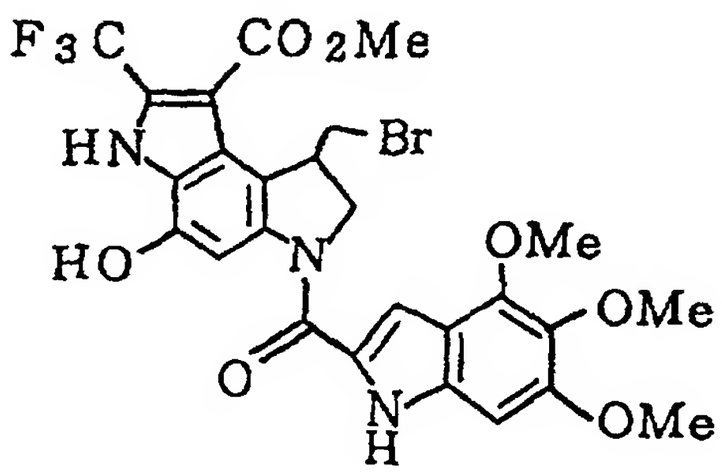


[0089] In 1 ml of acetonitrile, was dissolved 4.6 mg (9 μmol) of methyl 6-trifluoromethyl-2-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-1,2,8,8a-tetrahydrocyclopropa[c]-pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate. Thereto 0.5 ml of 1M hydrobromic acid was added, and the mixture was stirred for 6 hours. Then 1 ml of aqueous 0.5M potassium dihydrogenphosphate solution was added thereto, and the mixture was extracted with methylene chloride. The extract was washed with water, and saturated sodium chloride solution successively, and was dried over anhydrous sodium sulfate. The solvent was removed by distillation, and the residue was purified by silica gel column chromatography (hexane : ethyl acetate = 1 : 2). Thereby, methyl 1-bromomethyl-5-hydroxy-7-trifluoromethyl-3-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared in a pale yellow crystalline state in a yield of 4.7 mg (89 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ: 3.21(1H, t, J=10Hz), 3.76(1H, m),3.92(3H, s),3.95(3H, s),3.99(3H, s),4.09(3H, s), 4.50-4.56(2H,m),4.71(1H,d,J=9Hz),6.90(1H,s), 6.99(1H,d,J=2Hz),8.01(1H,s),9.19(1H,s),9.48(1H,s), 11.45(1H,s)

(EXAMPLE 35)

[0090]

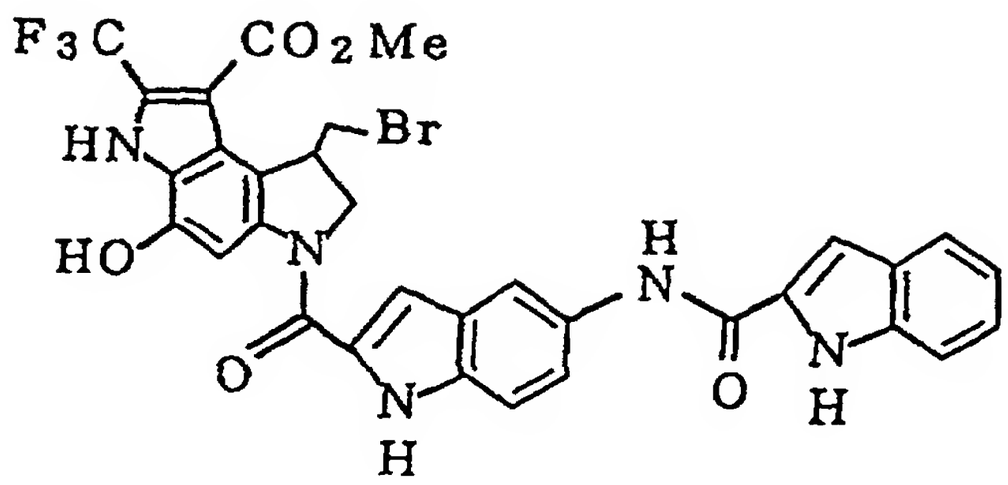


[0091] Methyl 1-bromomethyl-5-hydroxy-7-trifluoromethyl-3-(4,5,6-trimethoxy-1H-indol-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 4.8 mg (9 μmol) of methyl 6-trifluoromethyl-2-(4,5,6-trimethoxy-1H-indol-2-ylcarbonyly-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate in the same manner as above in a yield of 5.3 mg (97 %).

[0092] NMR ($CDCl_3$ + $DMSOd_6$) δ : 3. 23(1H, t, J=10Hz), 3. 76(1H, dd, J= 2Hz, J=10Hz), 3. 86(3H, s), 3. 88 (3H, s), 3. 99(3H, s), 4. 15(3H, s), 4. 49-4. 59(2H, m), 4. 73(1H, d, J=10Hz), 6. 67(1H, s), 7. 10(1H, d, J=2Hz), 8. 06(1H, s), 9. 11(1H, s), 9.84 (1H, s), 11. 32(1H, s)

(Example 36)

[0093]

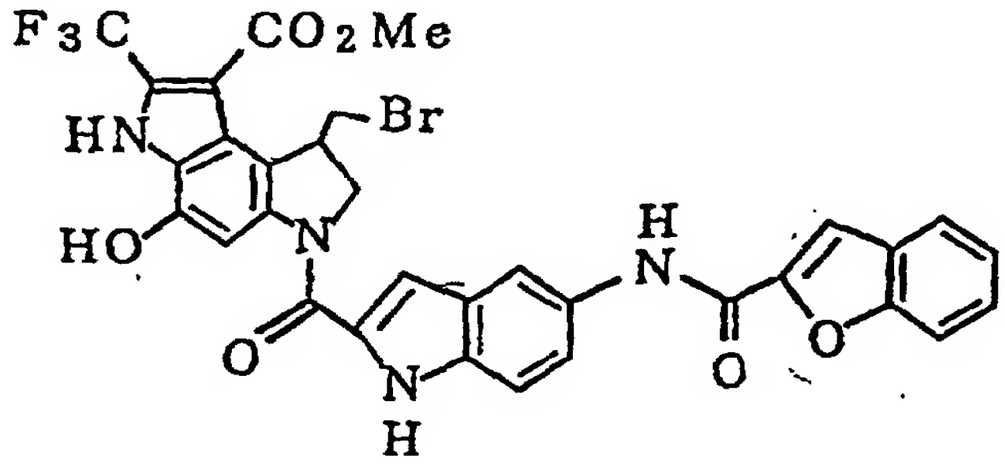


[0094] Methyl 1-bromomethyl-5-hydroxy-3-[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 3.7 mg (6 μmol) of methyl 2-[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate in the same manner as above in a yield of 3.9 mg (93 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ : 3. 23(1H, t, J=10Hz), 3. 77(1H, m), 3. 99 (3H, s), 4. 52-4. 60(2H, m), 4. 75(1H, d, J=10Hz), 7. 07(1H, s), 7. 15(1H, t, J=8Hz), 7. 24 (1H, br, s), 7. 28-7. 33(1H, m), 7. 46-7. 50(2H, m), 7. 53(1H, dd, J=2Hz, J=9Hz), 7.70(1H, d, J=8Hz), 8. 02(1H, s), 8. 21(1H, s), 8. 94(1H, s), 9. 12(1H, s), 9. 87(1H, s), 10. 00(1H, s), 11. 38(1H, s)

(EXAMPLE 37)

[0095]

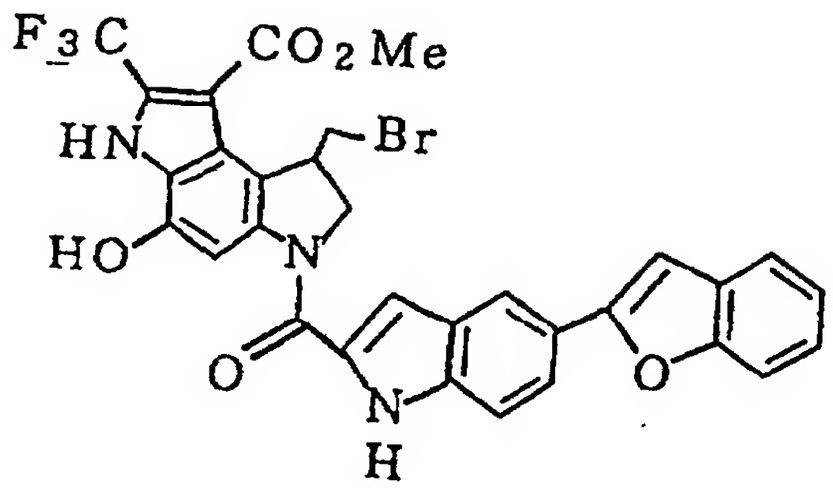


[0096] Methyl 3-[5-[(benzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1-bromomethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 9.4 mg (15 μmol) of methyl 2-[5-[(benzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate in the same manner as above in a yield of 9.2 mg (86 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ : 3. 24(1H, t, J=10Hz), 3. 78(1H, m), 4. 00 (3H, s), 4.51-4. 61(2H, m), 4. 75(1H, d, J=10Hz), 7. 09(1H, s), 7. 31-7.36 (2H, m), 7. 47 (1H, t, J=7Hz), 7. 51(1H, s), 7. 59-7. 62(2H, m), 7. 72(1H, d, J=8Hz), 8. 02(1H, br, s), 8. 25(1H, s), 8. 64(1H, s), 9. 13(1H, s), 9. 94(1H, s), 11. 39(1H, s)

(EXAMPLE 38)

[0097]

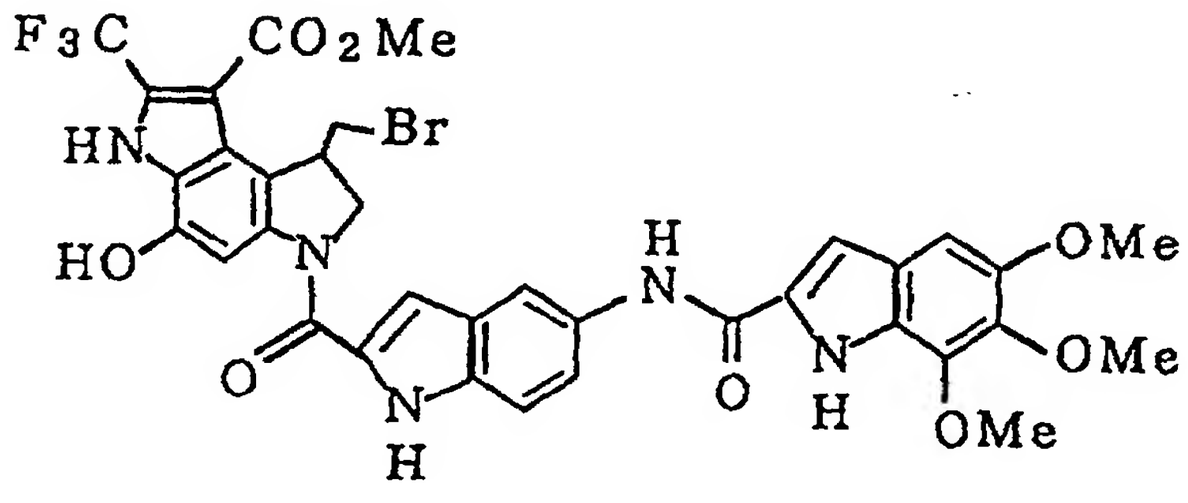


[0098] Methyl 3-(5-(benzofuran-2-yl)-1H-indol-2-ylcarbonyl)-1-bromomethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 5.6 mg (10 μmol) of methyl 3-(5-(benzofuran-2-yl)-1H-indol-2-ylcarbonyl)-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate in the same manner as above in a yield of 6.2 mg (98 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ : 3. 24(1H, t, J=10Hz), 3. 77(1H, m), 3. 99 (3H, s), 4. 52-4. 62(2H, m), 4. 76(1H, d, J=10Hz), 7. 00(1H, s), 7. 14(1H, s), 7. 21-7. 28 (2H, m), 7. 53(1H, d, J=8Hz), 7. 58(1H, d, J=8. 3Hz), 7. 81(1H, d, J=9Hz), 8. 02(1H, s), 8. 27(1H, s), 9. 21(1H, d, J=2Hz), 10. 40(1H, br, s), 10. 80(1H, br), 11. 57(1H, br, s)

(EXAMPLE 39)

[0099]

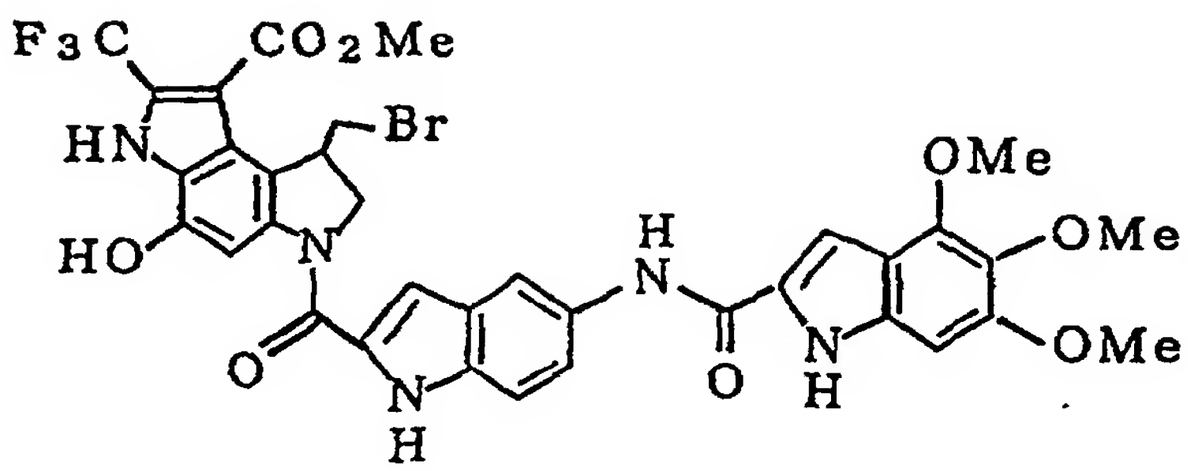


[0100] Methyl 1-bromomethyl-5-hydroxy-7-trifluoromethyl-3-[5-[(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 6.0 mg (9 μmol) of methyl 6-trifluoromethyl-2-[5-[(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate in the same manner as above in a yield of 6.5 mg (97 %).

NMR ($CDCl_3$ +$DMSOd_6$) δ :3. 24(1H, t, J=10Hz), 3. 76(1H,m), 3. 91 (3H, s), 3. 94(3H, s), 3. 99(3H, s), 4.10(3H, s), 4. 49-4.60(2H, m), 4. 74(1H, d, J=10Hz), 6. 88(1H, s), 7. 05(1H, s), 7. 23(1H, s), 7. 48(1H, d, J=9Hz), 7. 54(1H, dd, J=2Hz, J=9Hz), 8. 01(1H, br, s), 8. 21(1H, s), 9. 40(1H, s), 10. 16(1H, s), 10. 27(1H, s), 11. 63(1H,s)

(EXAMPLE 40)

[0101]

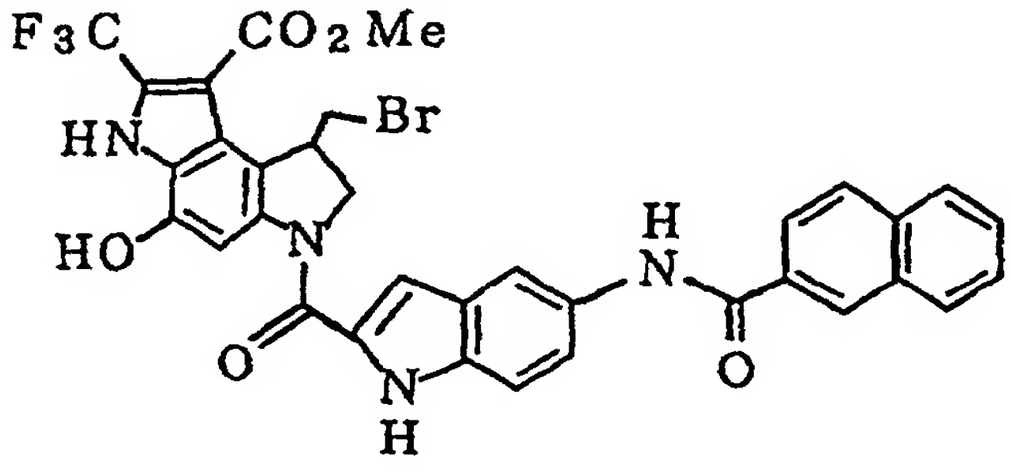


[0102] Methyl 1-bromomethyl-5-hydroxy-7-trifluoromethyl-3-[5-[(4,5,6-trimethoxy-1H-indol-2-ylcarbonyl)amino]-1H-indol 2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 3.8 mg (5 μmol) of methyl 6-trifluoromethyl-2-[5-[(4,5,6-trimethoxy-1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate in the same manner as above in a yield of 4.2 mg (99 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ : 3. 22(1H, t, J=10Hz) , 3. 76(1H, m), 3. 84 (3H, s) , 3. 87(3H, s), 3. 98(3H, s), 4. 14 (3H, s), 4. 50-4. 57(2H, m), 4. 73(1H, d, J=10Hz), 6. 66(1H, s), 7.04(1H, s), 7.34(1H, s), 7.44(1H, d, J=8Hz), 7.51(1H, d, J=8Hz), 8. 05 (1H, br, s), 8.19(1H, s), 8. 98(1H,s), 9. 18(1H, s), 10. 12(2H, br, s), 11. 42(1H, s)

(EXAMPLE 41)

[0103]

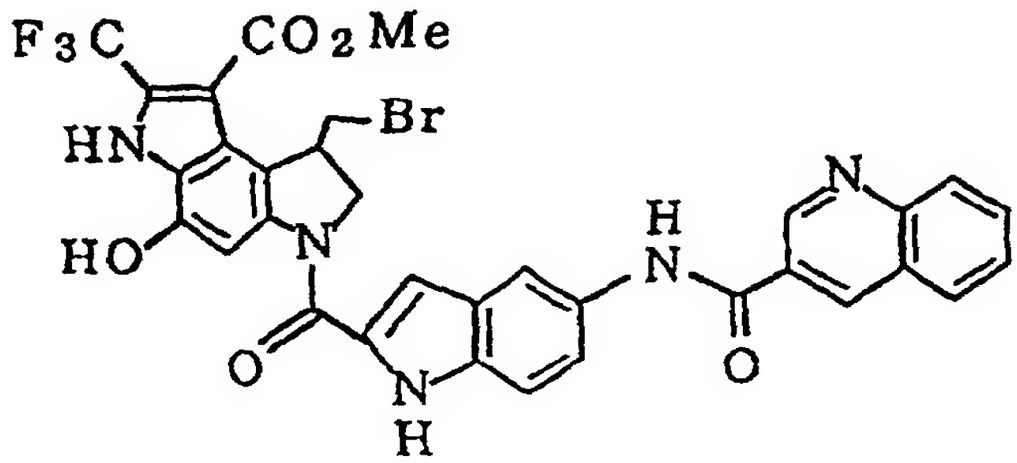


[0104] Methyl 1-bromomethyl-5-hydroxy-3-[5-[(naphthalene-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 2.9 mg (5 μmol) of methyl 3-[5-[(naphthalene-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate in the same manner as above in a yield of 3.2 mg (97 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ : 3. 23(1H,t,J=10Hz), 3. 77(1H, m), 3. 99 (3H, s), 4. 49(1H, m), 4. 58(1H, t, J=10Hz), 4. 74(1H, d, J=11Hz), 7. 07(1H, s), 7. 50(1H, d, J=9Hz), 7. 55-7. 60(3H, m), 7. 91(1H, d, J=7Hz),7. 95(1H, d, J=9Hz), 7. 99(1H, d, J= 7Hz), 8. 07(1H, d, J=8Hz), 8. 25(1H, s), 8. 53(1H, s), 9. 27(1H, s), 9. 35(1H, s), 10. 23 (1H, s), 10. 94 (1H, s), 11. 61(1H, s)

(EXAMPLE 42)

[0105]

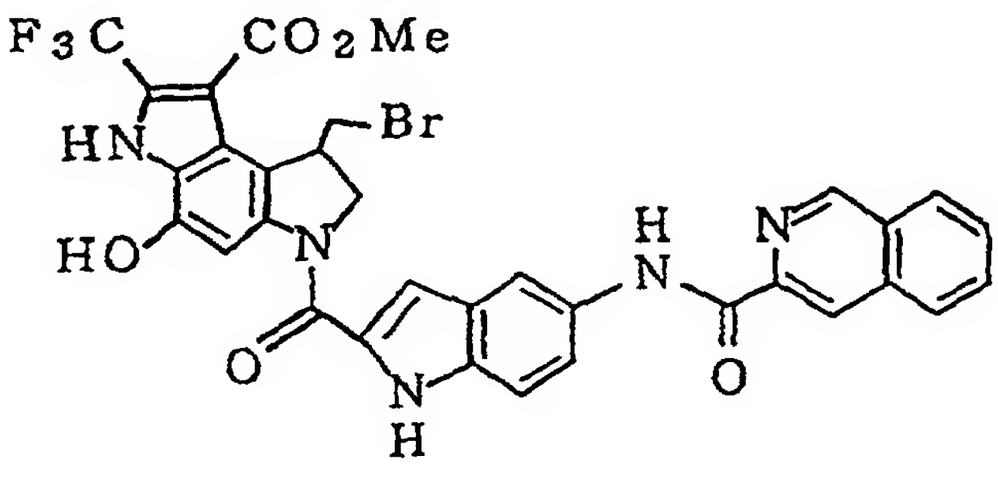


[0106] Methyl 1-bromomethyl-5-hydroxy-3-[5-[(quinoline-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 2.7 mg (4 μmol) of methyl 3-[5-[(quinoline-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate in the same manner as above in a yield of 2.6 mg (84 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ : 3. 24(1H, t, J=10Hz),3. 76(1H, m),3. 99 (3H, s),4. 51-4. 58(2H, m), 4. 75(1H, d, J=10. 3Hz), 7. 06(1H, s), 7. 45(1H, d, J=9Hz), 7. 58(1H, d, J=8Hz), 7. 64(1H, t, J=8Hz), 7. 83(1H, t, J=8Hz), 7. 97(1H, d, J=7Hz), 8. 03(1H, br, s) , 8.18(1H, d, J=8Hz), 8. 24(1H, s), 8. 85(1H, s), 9. 29(1H, s), 9. 53(1H, s), 9. 65 (1H, br, s), 10. 01(1H, br, s), 11. 44(1H, br, s)

(EXAMPLE 43)

[0107]

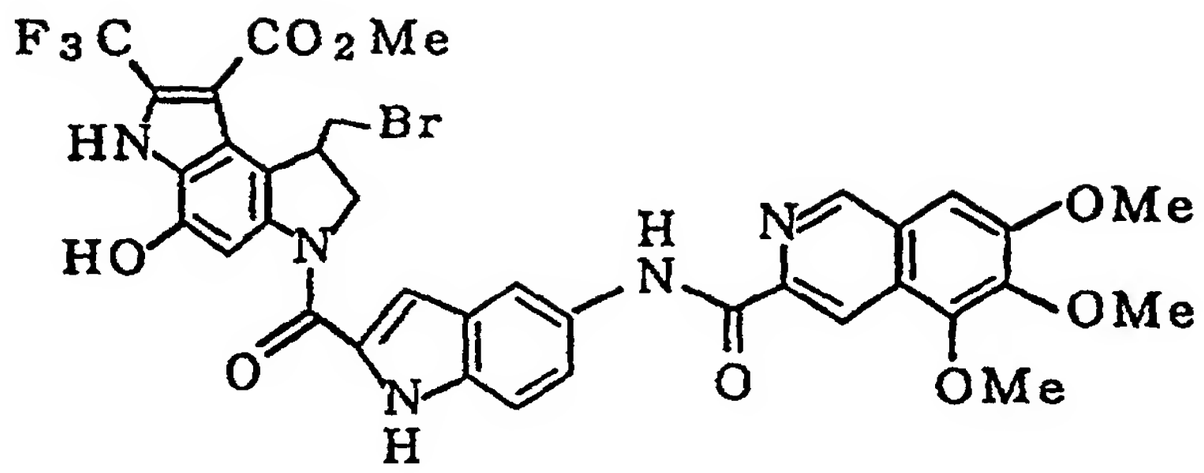


[0108] Methyl 1-bromomethyl-5-hydroxy-3-[5-[(isoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 3.1 mg (5 μmol) of methyl 3-[5-[(isoquinolin-3-ylcarbonyl]amino]-1H-indol-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate in the same manner as above in a yield of 3,5 mg (98 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ : 3. 24(1H, t, J=10Hz), 3. 78(1H, d, J= 9Hz), 3. 99(3H, s), 4. 51-4. 59(2H, m), 4. 76 (1H, d, J=10Hz), 7. 09(1H, s), 7. 51 (1H, d, J =9Hz), 7. 62(1H, d, J=9Hz), 7. 76(1H, t, J=8Hz), 7. 83(1H, t, J=8Hz), 8. 03-8.12(4H, m), 8. 40(1H, s), 8. 80(1H, s), 9. 26(1H, s), 10. 02(1H, br), 10. 34(1H, s), 11. 44(1H, s)

(EXAMPLE 44)

[0109]

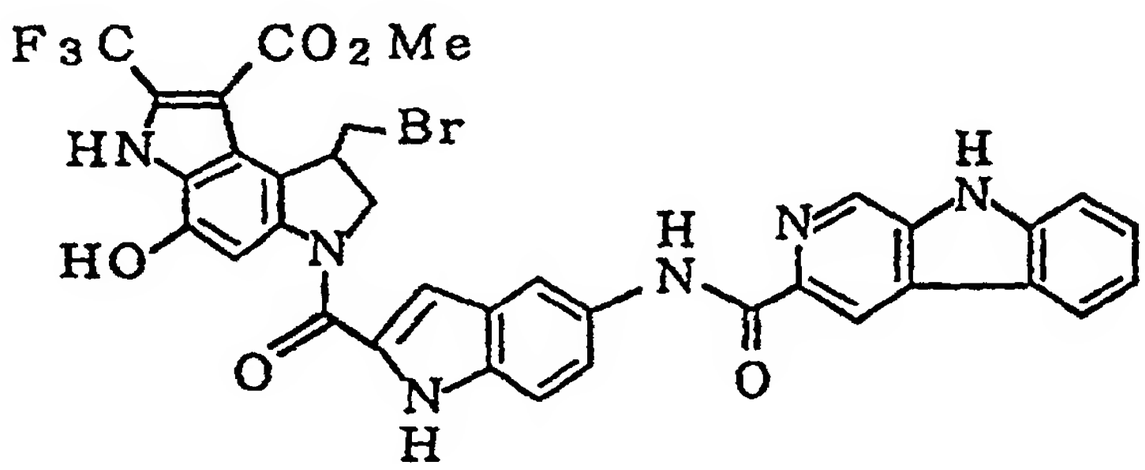


[0110] Methyl 1-bromomethyl-5-hydroxy-7-trifluoromethyl-3-[5-[(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 7.0 mg (10 μmol) of methyl 6-trifluoromethyl-2-[5-[(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate in the same manner as above in a yield of 7.4 mg (95 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ : 3. 25(1H, t, J=10Hz), 3. 77(1H, m), 3. 99 (3H, s), 4. 05(3H, s), 4. 07(3H, s), 4. 12 (3H, s), 4. 48(1H, m), 4. 59(1H, t, J=8Hz), 4. 74 (1H, d, J=11Hz), 7. 07(1H, s), 7. 19(1H, s), 7. 54(1H, d, J=9Hz), 7. 60 (1H, dd, J=2Hz, J= 9Hz), 7. 98(1H, br, s), 8. 36 (1H, s), 8. 85(1H, s), 9. 07(1H, s), 9. 39(1H, s), 14. 27(1H, s), 10. 66 (1H, s), 11. 85(1H, s)

(EXAMPLE 45)

[0111]

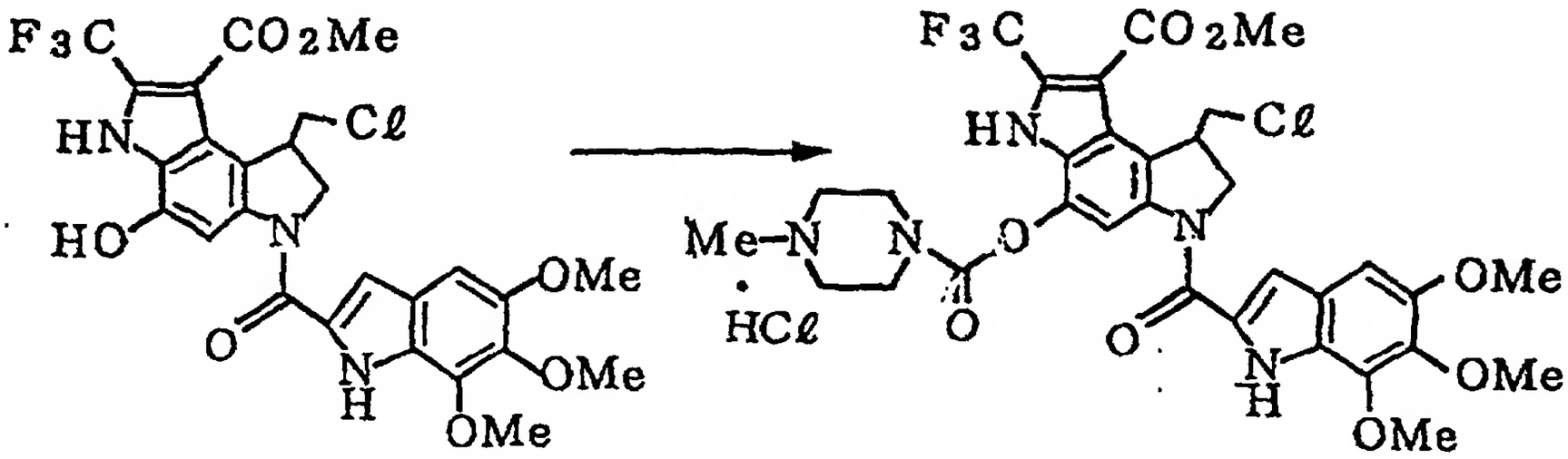


[0112] Methyl 1-bromomethyl-5-hydroxy-3-[5-[(9H-pyrido[3,4-b]indol-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 5.9 mg (9 μmol) of methyl 2-[5-[(9H-pyrido[3,4-b]indol-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate in the same manner as above in a yield of 6.4 mg (96 %).

NMR ($CDCl_3$ + $DMSOd_6$) δ : 3. 24(1H, t, J=10Hz), 3. 76(1H, m), 3. 99 (3H, s), 4. 51(1H, m), 4. 57(1H, t, J=10Hz), 4. 76(1H, d, J=11Hz), 7. 10(1H,s), 7. 33(1H, m), 7. 51(1H, d, J=9Hz), 7. 54-7. 67(3H, m), 8. 03(1H, br, s), 8.23(1H, d, J=9Hz), 8. 37 (1H, s), 8. 88(1H, s), 9. 02(1H, s), 9. 25(1H, s),10. 10(1H, br), 10. 24(1H, s), 10. 80(1H, br), 11. 51(1H, br)

(EXAMPLE 46)

[0113]



[0114] 5.0 Milligrams (9 μmol) of methyl 1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indol-8-carboxylate was suspended in methylene chloride. Thereto, 2.3 mg (11 μmol) of p-nitrophenyl chloroformate and 1.6 μl (11 μmol) of triethylamine was added, and the mixture was stirred under ice cooling for 50 minutes. Further thereto, 1.4 μl (13 μmol) of N-methylpiperazine was added and the mixture was stirred overnight at room temperature.

[0115] The reaction mixture was diluted with chloroform. The diluted mixture was washed with water, 10% sodium hydrogencarbonate, and water successively, and dried over anhydrous sodium sulfate. The solvent was distilled off, and the residue was purified by silica gel column chromatography chloroform : methanol = 8 : 1). Thereby, methyl 1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-3-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in a colorless crystal state in a yield of 4.5 mg (74 %).

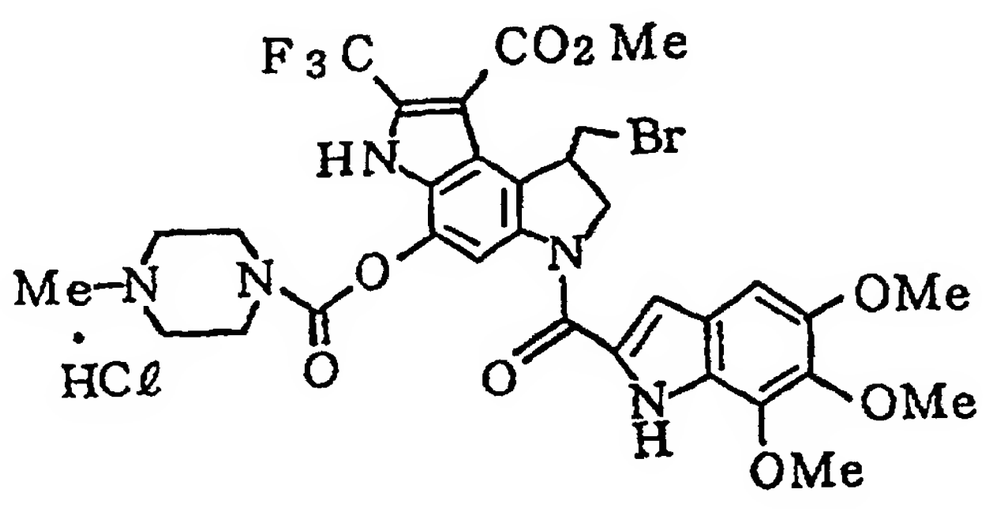
NMR ($CDCl_3$) δ : 2. 38(3H, s), 2. 46-2. 52(4H, m), 3. 39(1H, t, J=10Hz), 3. 59-3. 72(2H, m), 3. 76-3. 83(2H, m), 3. 91(1H, m), 3. 92(3H, s), 3. 95(3H, s), 3. 99(3H, s), 4. 09(3H, s), 4. 54-4.62(2H, m), 4.76-4. 82(1H, m), 6. 89(1H, s), 7.01(1H, d, J=2Hz), 8. 36(1H, s), 9. 33(1H, s), 9. 57(1H, s)

[0116] To 3.0 mg (4.3 μmol) of the resulting crystal, was added 0.4 ml of 3M hydrogen chloride-ethyl acetate, and the solvent was distilled off. The residue was washed with ether to give 3.1 mg (97 %) of the hydrochloride salt thereof in a colorless crystal state.

NMR ($DMSOd_6$) δ : 2. 85(3H, br, s), 3.10-3. 26(3H, m),3. 46-3. 65(4H, m), 3. 80(3H, s), 3. 82(3H, s),3. 90(3H, s),3. 94(3H, s),3. 93-3. 96(1H, m),4. 16(1H, m), 4. 35-4. 81(3H, m),4. 72(1H, dd, J=9Hz, J=11Hz),6. 97(1H, s),7. 04 (1H, s),8. 14(1H, s), 10. 78(1H, br),11. 39(1H, s),13.16(1H, s)

(EXAMPLE 47)

[0117]

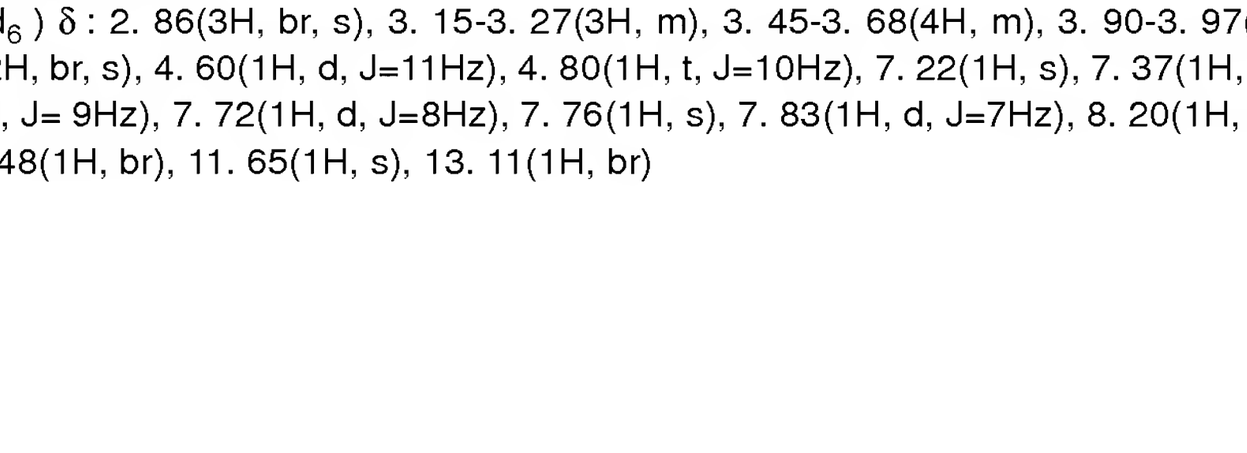


[0118] Methyl 1-bromomethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-3-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 11.09 mg (18 μmol) of methyl 1-bromomethyl-5-hydroxy-7-trifluoromethyl-3-(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as above in a yield of 6.9 mg (52 %).

NMR ($CDCl_3$) δ : 2. 37(3H, s), 2. 47-2. 58(4H, m), 3. 26(1H, t, J=10Hz), 3. 60-3. 70(2H, m) , 3. 76-3. 83(3H, m), 3. 92(3H, s), 3. 95(3H, s), 4. 00(3H, s), 4. 09(3H, s), 4. 56-4. 67(2H,m), 4. 77(1H, d, J=10Hz), 6. 90(1H, s), 7. 01(1H, d, J=2Hz), 8. 36(1H, s), 9. 34(1H, s), 9. 59(1H, s)
Hydrochloride salt: 4.8 mg (96 %)
NMR ($DMSOd_6$) δ : 2. 86(3H, br, s), 3. 15-3. 28(3H, m), 3. 43-3. 70(4H, m), 3. 77-3. 82(1H, m), 3. 81(3H, s), 3. 83(3H, s), 3. 92(3H, s), 3. 96(3H, s), 4.16(1H, m), 4. 35-4. 53(3H, m), 4. 72(1H, t, J=10Hz), 6. 96(1H, s), 7. 03(1H, s), 8.14(1H, s), 8. 30(1H, s), 11. 35(1H, s), 13. 12(1H, s)

(EXAMPLE 48)

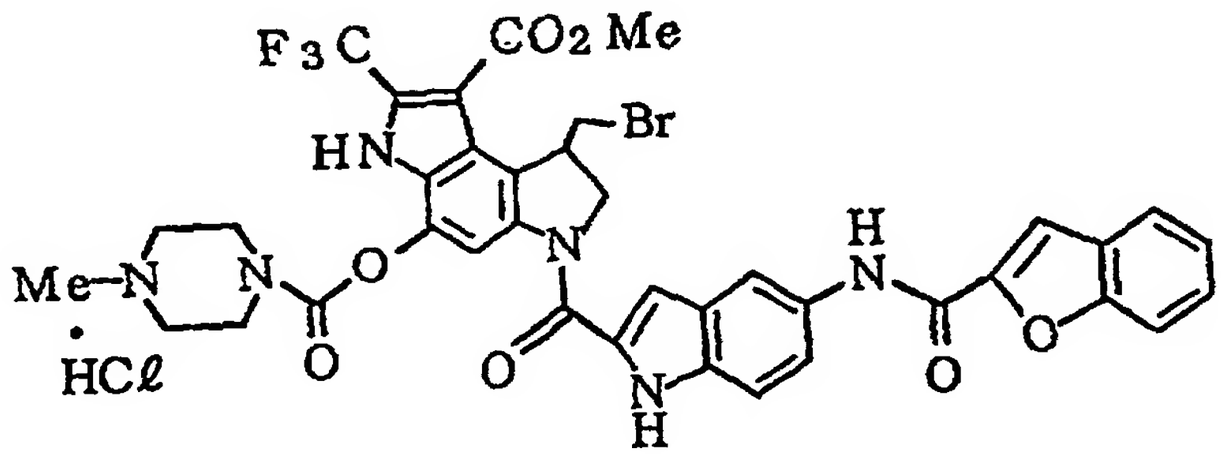
[0119]



[0120] Methyl 3-[5-(benzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 5.0 mg (8 μmol) of methyl 3-[5-(benzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1-chloromethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as above in a yield of 4.8 mg (80 %).
NMR ($CDCl_3$) δ : 2.37(3H,s), 2. 46-2. 60(4H, m), 3. 40(1H, dd, J=9Hz, J= 11Hz), 3. 60-3. 72(2H, m), 3. 77-3. 92 (3H, m), 3. 99(3H, s), 4. 56-4. 67 (2H, m), 4. 80(1H, m), 7. 08(1H, s), 7. 34(1H, t, J=7Hz), 7. 42-7. 49(3H, m), 7.59(1H, d, J=8Hz), 7. 62(1H, s), 7.73(1H, d, J=8Hz), 8. 23(1H, s), 8. 37(1H, s), 8. 42(1H, s), 9. 34(1H, s), 9. 72(1H, s)
Hydrochloride salt: 3.5 mg (97 %)
NMR ($DMSOd_6$) δ : 2. 86(3H, br, s), 3. 15-3. 27(3H, m), 3. 45-3. 68(4H, m), 3. 90-3. 97(1H, m), 3. 92(3H, s), 4.18(1H, m), 4. 43(2H, br, s), 4. 60(1H, d, J=11Hz), 4. 80(1H, t, J=10Hz), 7. 22(1H, s), 7. 37(1H, t, J=7Hz), 7. 49-7. 52 (2H, m), 7. 63(1H, d, J= 9Hz), 7. 72(1H, d, J=8Hz), 7. 76(1H, s), 7. 83(1H, d, J=7Hz), 8. 20(1H, s), 8. 23(1H, s), 8. 30 (1H, d, J=5Hz), 10. 48(1H, br), 11. 65(1H, s), 13. 11(1H, br)

(EXAMPLE 49)

[0121]



[0122] Methyl 3-[5-(benzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1-bromomethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 6.9 mg (10 μmol) of methyl 3-[5-[(benzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1-bromomethyl-5-hydroxy-7-trifluor-

omethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as above in a yield of 6.8 mg (83 %).

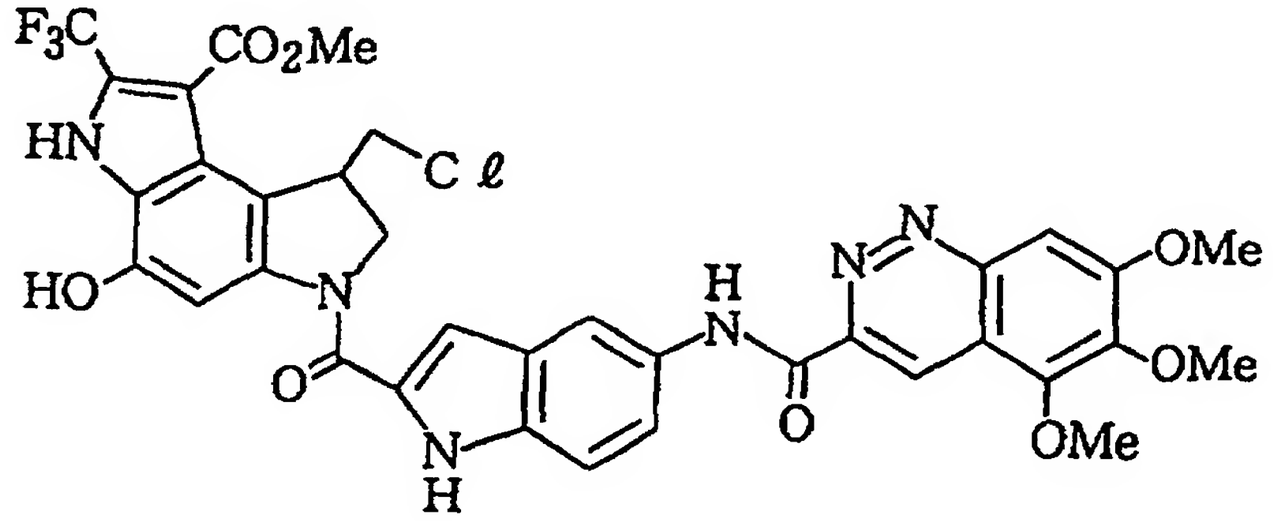
NMR ($CDCl_3$) δ : 2. 37(3H, s), 2. 46-2. 60(4H, m), 3. 27(1H, t, J=10Hz), 3. 61-3. 71(2H, m), 3. 73-3. 85(3H, m), 4. 00(3H, s), 4. 56-4. 69(2H, m), 4. 77(1H, d, J= 9Hz), 7. 08(1H, s), 7. 34(1H, t, J=7Hz), 7. 47(3H, m), 7. 59(1H, d, J=9Hz), 7. 63(1H, s), 7. 73(1H, d, J=7Hz), 8. 23(1H, m), 8. 37(1H, s), 8. 42(1H, s), 9. 34(1H, s), 9. 73(1H, br)

Hydrochloride salt: 5.4 mg (98 %)

NMR (DMSO d_6) δ : 2. 87(3H, br, s), 3. 12-3. 30(3H, m), 3. 45-3. 63(4H, m), 3. 84(1H, dd, J=3Hz, J=10Hz), 3. 93(3H, s).4. 17(1H, m), 4. 35-4. 52(2H, m), 4. 58(1H, d, J=11Hz), 4. 81(1H, t, J=10Hz), 7. 21(1H, d, J=2Hz), 7. 38(1H, t, J=7Hz), 7. 49-7. 53(2H, m), 7. 83(1H, dd, 7=2Hz, J=9Hz), 7. 73(1H, d, J=8Hz), 7. 77(1H, s), 7. 83(1H, d, J=7Hz), 8. 20(1H, s), 8. 23(1H, s), 8. 31(1H, s), 10. 49(1H, s), 11. 65(1H, br), 13. 13(1H, br)

(EXAMPLE 50)

[0123]

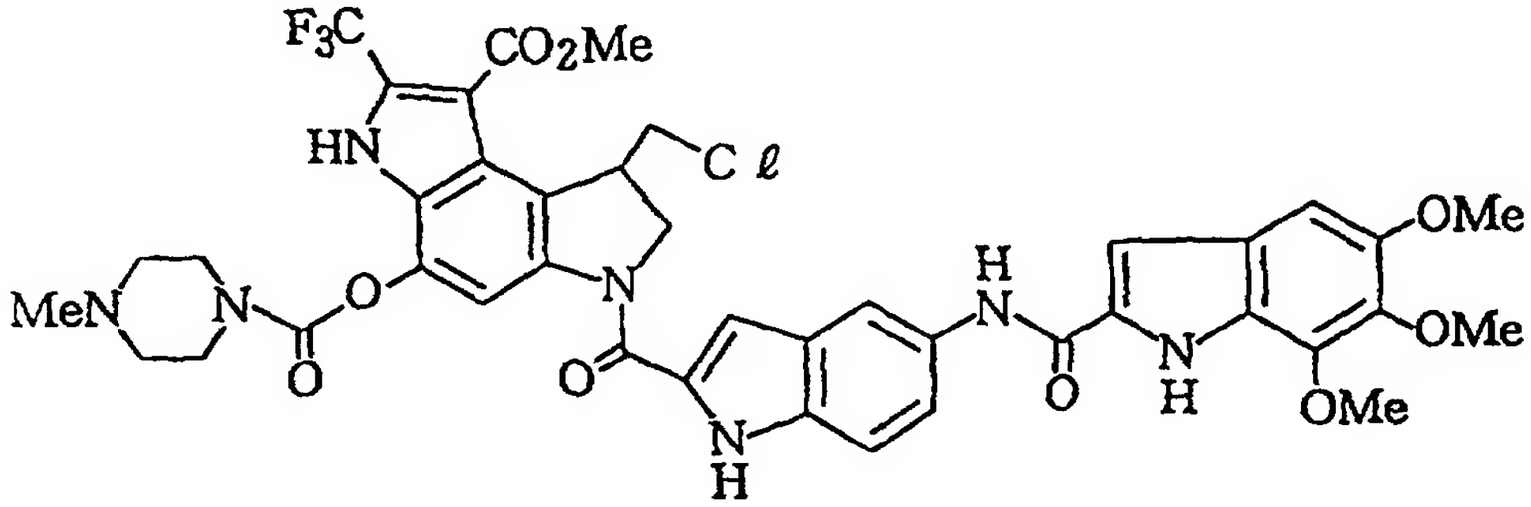


[0124] Methyl 1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-[5-[(5,6,7-trimethoxycinnolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-6-carboxylate was prepared by using 9.7 mg (23 μmol) of 5-(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 13.4 mg (77 %).

NMR (DMSO d_6) δ : 3. 41(1H, t, J=10Hz),3. 91(1H, d, J=10Hz),3. 99(3H, s),4. 090(3H, s),4. 094(3H, s),4. 15(3H, s),4, 45(1H, m),4. 60(1H, t, J=10Hz), 4.78 (1H, d, J=11Hz), 7. 08(1H, s),7. 52(1H, d, J=9Hz),7. 60(1H, d, J=9Hz),7. 68 (1H, s), 8. 06(1H, brs),9. 36(1H, s),9. 97(1H, s),9. 39(1H, br),10. 44(1H, br),10. 47(1H, s),11. 67(1H, br)

(EXAMPLE 51)

[0125]

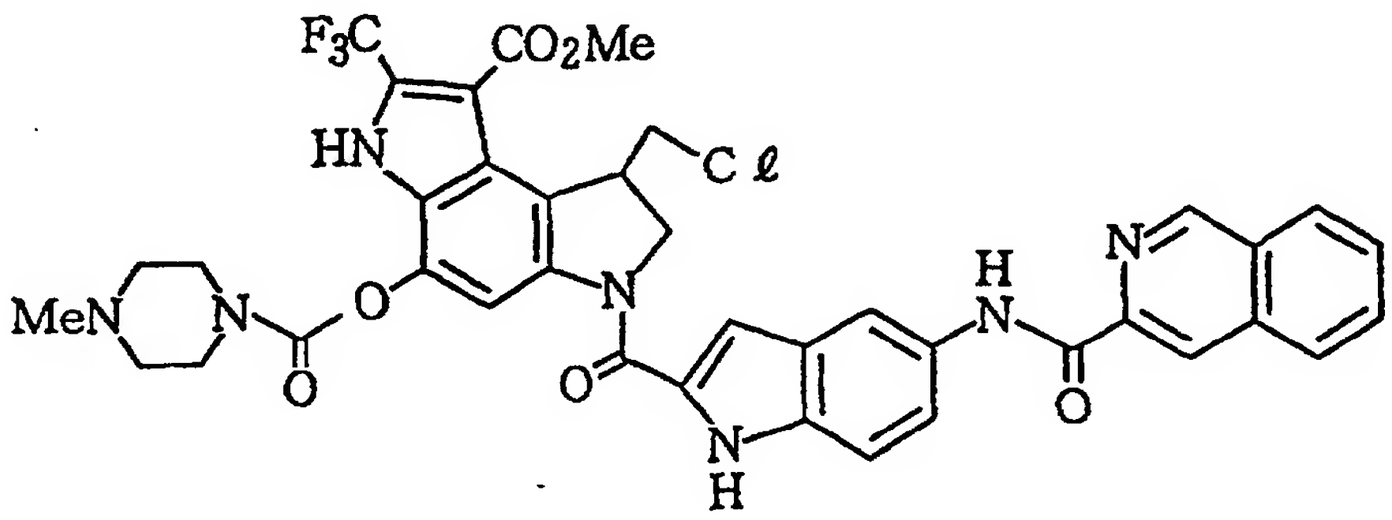


[0126] Methyl 1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-3-[5-[(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 12.0 mg (16 μmol) of methyl 1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-[5-[(5,6,7-trimethoxy-1H-indol-2-yl-carbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 46 in a yield of 6.3 mg (45 %).

NMR ($CDCl_3$) δ : 2. 36(3H, s), 2. 52(4H, s), 3. 36(1H, brs), 3. 63~3. 85 (5H, m), 3. 90(3H, s), 3. 94(3H, s), 3. 96(3H, s), 4. 09(3H, s), 4. 51~4.59(2H, m), 4. 73 (1H, d, J=10Hz), 6. 82(1H, s), 7. 00(1H, s), 7. 13(1H, brs), 7. 42~7. 44(2H, m), 8. 19(1H, brs), 8. 30(1H, s), 9. 05(1H, brs), 9. 79(1H, brs), 9. 87(1H, brs), 11.48(1H, brs)

(EXAMPLE 52)

[0127]

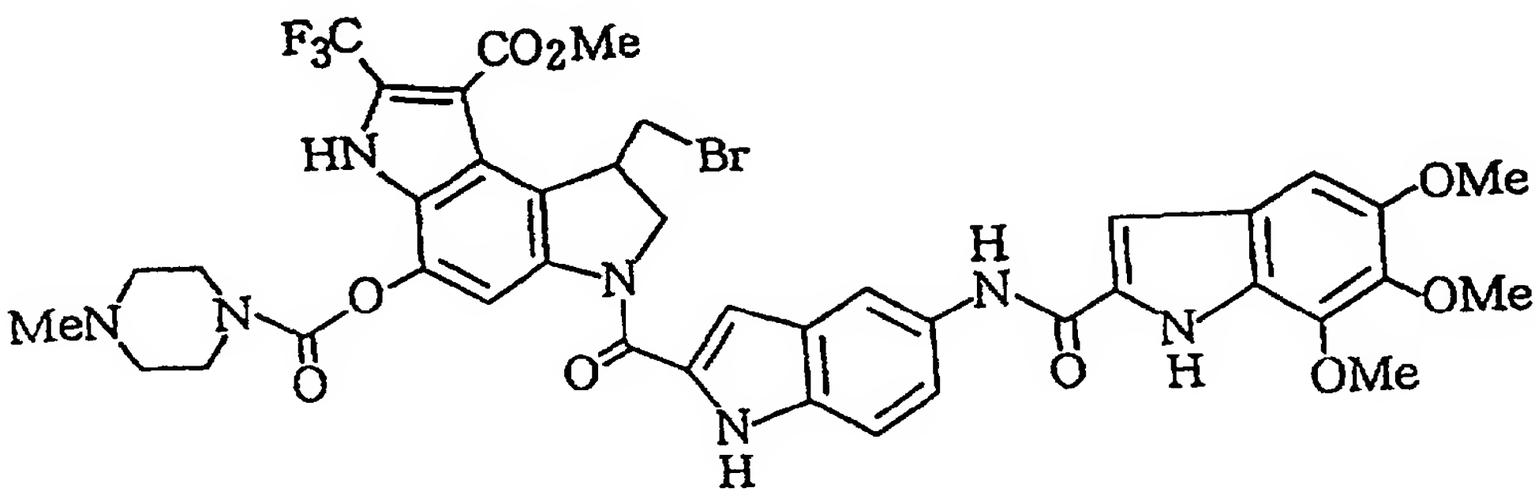


[0128] Methyl 1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-3-[5-[(isoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 7.6 mg (11 μmol) of methyl 1-chloromethyl-5-hydroxy-3-[5-[(isoquinolin-3-ylcarbonyl)amino)]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 46 in a yield of 3.8 mg (43 %).

NMR ($CDCl_3$) δ : 2. 35(3H, s), 2. 52(4H, s), 3. 38(1H, t, J=9Hz), 3. 67(2H, s), 3. 83~3. 87 (3H, m), 3. 98(3H, s), 4. 56~4. 62(2H, m), 4. 77(1H, d, J=9Hz), 7. 04(1H, s), 7. 41(1H, d, J=9Hz), 7. 51(1H, dd, J=2Hz, J=9Hz), 7. 74(1H, t, J=7Hz), 7.81(1H, t, J =7Hz), 8. 05(1H, d, J=8Hz), 8. 09(1H, d, J=8Hz), 8. 33(1H, s), 8. 38(1H, s), 8. 76(1H, s), 9. 25 (1H, s), 9. 41(1H, s), 10. 02(1H, br), 10. 27(1H, s)

(EXAMPLE 53)

[0129]

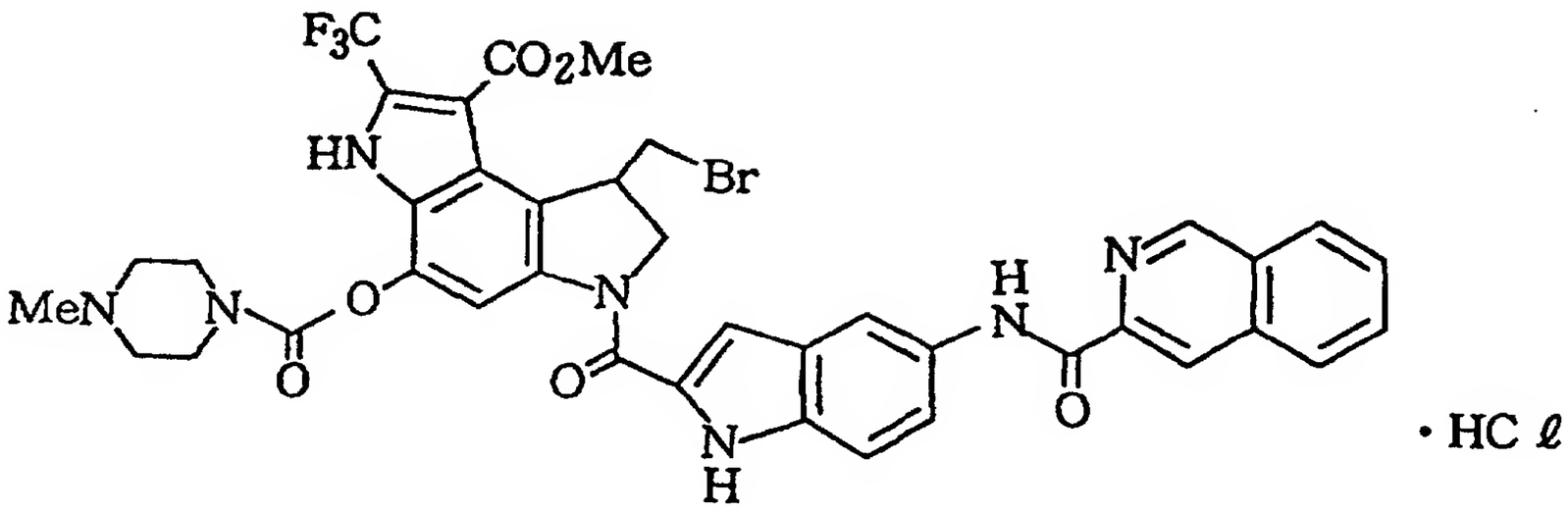


[0130] Methyl 1-bromomethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-3-[5-[(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 9.9 mg (13 μmol) of methyl 1-bromomethyl-5-hydroxy-7-trifluoromethyl-3-[5-[(5,6,7-trimethoxy-1H-indol-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 46 in a yield of 7.0 mg (61 %).

NMR ($CDCl_3$) δ : 2.36(3H,s), 2. 53 (4H, brs), 3. 23(1H, brs), 3. 63~3. 84 (5H, m), 3. 91(3H, s), 3. 94(3H, s), 3. 98(3H, s), 4. 09(3H, s), 4.58(2H, brs), 4.72(1H, d, J=9Hz), 6. 83(1H, s), 7. 01(1H, s), 7. 15(1H, brs), 7. 42(2H, m), 8. 21(1H, brs), 8. 30 (1H, s), 9. 13(1H, brs), 9. 83(1H, brs), 9. 92(1H, brs), 11.61(1H, brs)

(EXAMPLE 54)

[0131]

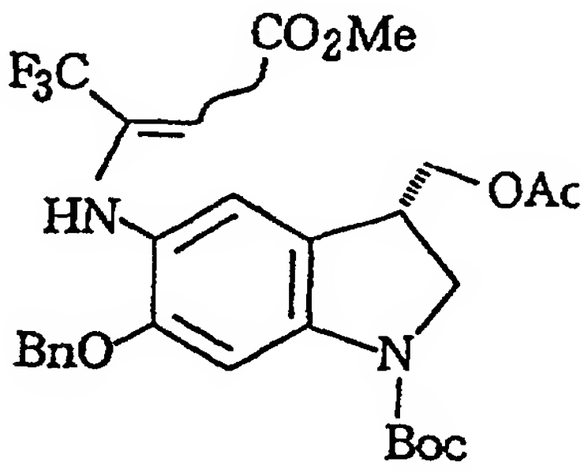


[0132] Methyl 1-bromomethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-3-[5-[(isoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate hydrochloride salt was prepared by using 13.0 mg (18 μmol) of methyl 1-bromomethyl-5-hydroxy-3-[5-[(isoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 46 in a yield of 2.2 mg (13 %).

NMR ($DMSOd_6$) δ : 2. 86(3H, brs), 3. 21~3. 61(7H, m), 3. 85(1H,m), 3. 93 (3H, s), 4. 16(1H, m), 4. 42~4. 48 (2H, m), 4. 59(1H, d, J=11Hz), 4. 83(1H, t, J=9Hz), 7. 22(1H, s), 7. 52(1H, d, J=9Hz), 7. 76(1H, d, J=9Hz), 7. 86(1H, t, J=8Hz), 7. 93 (1H, t, J= 8Hz), 8. 21(1H, s), 8. 26(1H, d, J=8Hz), 8. 32(1H, d, J=6Hz), 8. 41(1H, s), 8. 74 (1H, s), 9. 50(1H, s), 10. 71(1H, s), 10. 84(1H, br), 11. 65(1H, s), 13. 17(1H, s)

(EXAMPLE 55)

[0133]

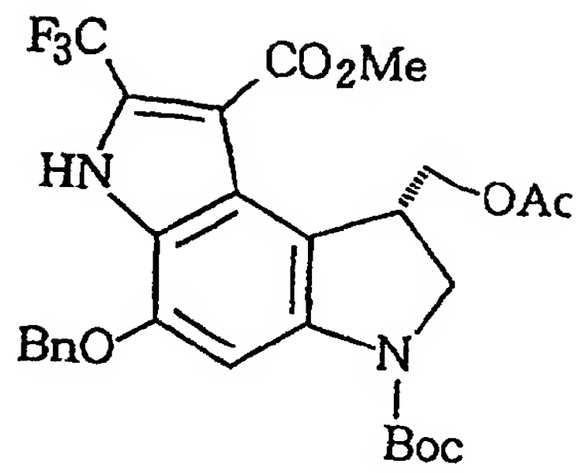


[0134] Methyl 3-((3S)-3-acetoxymethyl-6-benzyloxy-1-t-butoxycarbonyl-2,3-dihydro-1H-indol-5-yl)amino-3-trifluoromethylacrylate was prepared from (3S)-3-acetoxymethyl-5-amino-6-benzyloxy-1-(t-butoxycarbonyl)-2,3-dihydroindole in the same manner as in Example 1.

$[\alpha]_D^{25}$ = +8.9° (c=0.53, chloroform)

(EXAMPLE 56)

[0135]

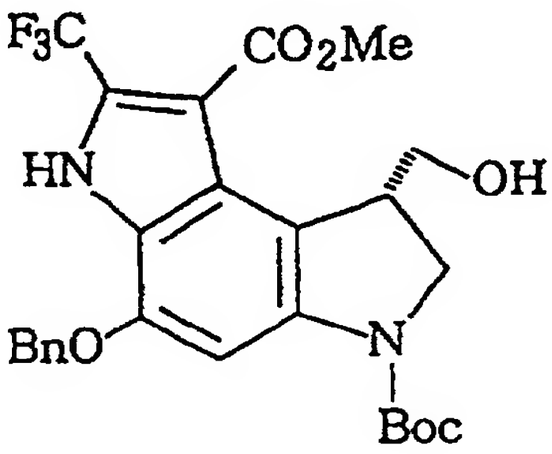


[0136] Methyl (1S)-1-acetoxymethyl-5-benzyloxy-3-t-butoxycarbonyl-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared from methyl 3-((3S)-3-acetoxymethyl-6-benzyloxy-1-t-butoxycarbonyl-2,3-dihydro-1H-indol-5-yl)amino-3-trifluoromethylacrylate in the same manner as in Example 2.

$[\alpha]_D^{25}$ = -70° (c=0.20, chloroform)

(EXAMPLE 57)

[0137]

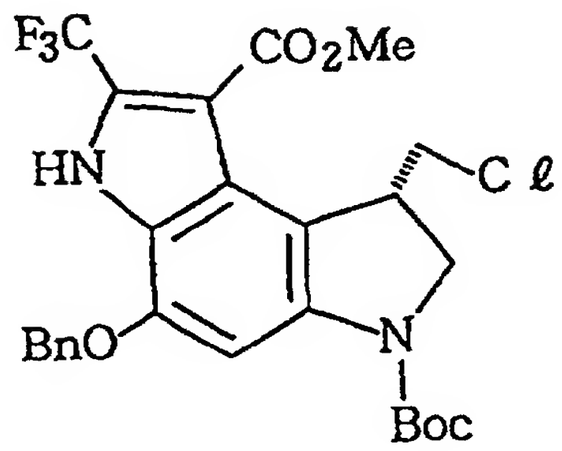


[0138] Methyl (1S)-5-benzyloxy-3-t-butoxycarbonyl-1-hydroxymethyl-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared from methyl (1S)-1-acetoxymethyl-5-benzyloxy-3-t-butoxycarbonyl-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 3.

$[\alpha]_D^{25}$ = -32° (c=0.45, chloroform)

(EXAMPLE 58)

[0139]

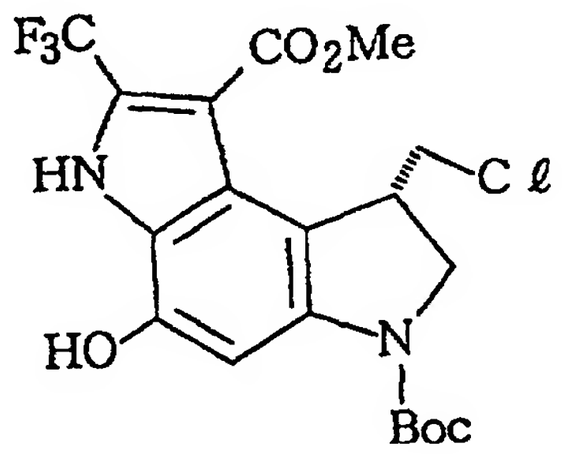


[0140] Methyl (1S)-5-benzyloxy-3-t-butoxycarbonyl-1-chloromethyl-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared from methyl (1S)-5-benzyloxy-3-t-butoxycarbonyl-1-hydroxymethyl-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo(3,2-e]indole-8-carboxylate in the same manner as in Example 4.

$[\alpha]_D^{23}$ = -60° (c=0.40, chloroform)

(EXAMPLE 59)

[0141]

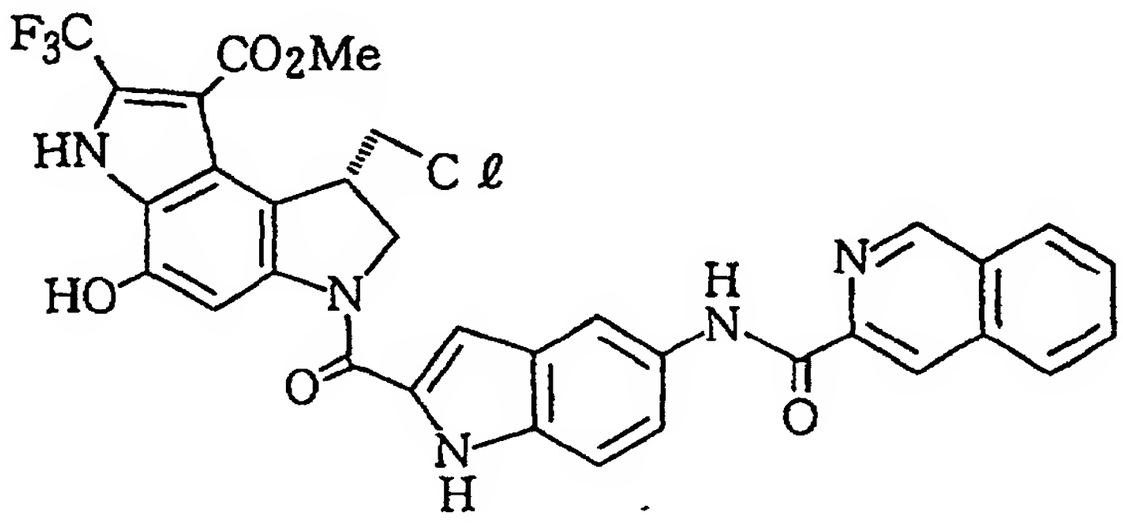


[0142] Methyl (1S)-3-t-butoxycarbonyl-1-chloromethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared from methyl (1S)-5-benzyloxy-3-t-butoxycarbonyl-1-chloromethyl-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 5.

$[\alpha]_D^{23}$ = -78° (c=0.32, chloroform)

(EXAMPLE 60)

[0143]



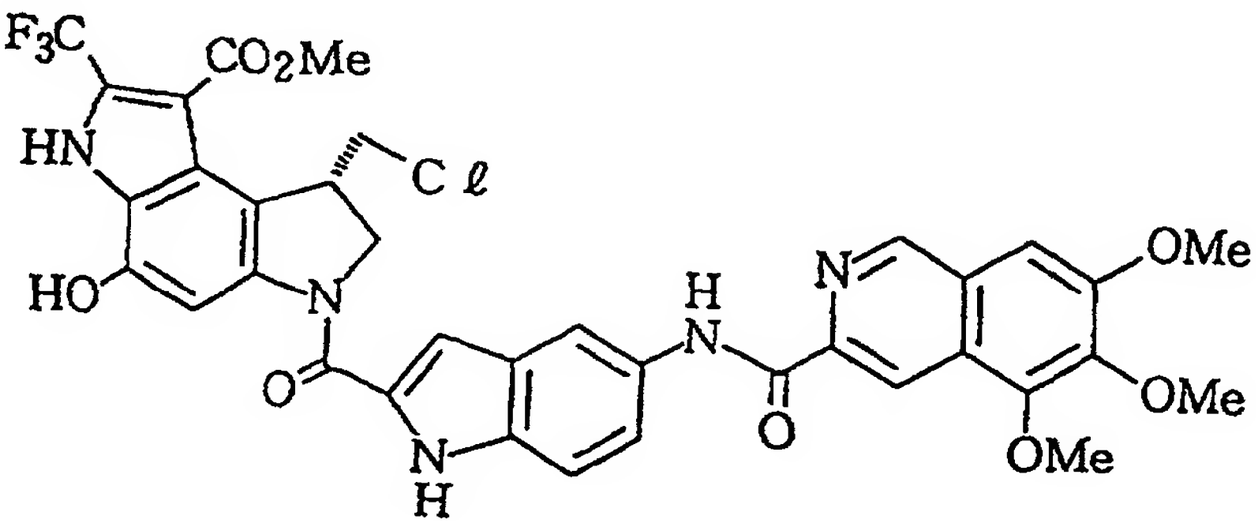
[0144] Methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-[(isoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 3-(5-isoquinolin-3-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6.

NMR (DMSO d_6) δ : 3. 52(1H, t, J=8Hz),3. 87(1H, m),3. 89(3H, s)14. 30 (1H, m),4. 56(1H, d, J=11Hz),4. 72(1H, t, J=8Hz),7. 18(1H, s),7. 50(1H, d, J=9Hz), 7. 73(1H, d, J=9Hz),7. 84(1H, t, J=7Hz),7. 91(1H, t, J=7Hz),7. 96(1H, s), 8. 25~8. 31(2H, m), 8. 39(1H, s),8. 73(1H, s),9. 48(1H, d, J=2Hz),10. 56(1H, brs),10. 68(1H, brs), 11. 72(1H, s), 13. 05(1H, brs)

$[\alpha]_D^{24}$ = +63° (c=0.24, tetrahydrofuran)

(EXAMPLE 61)

[0145]

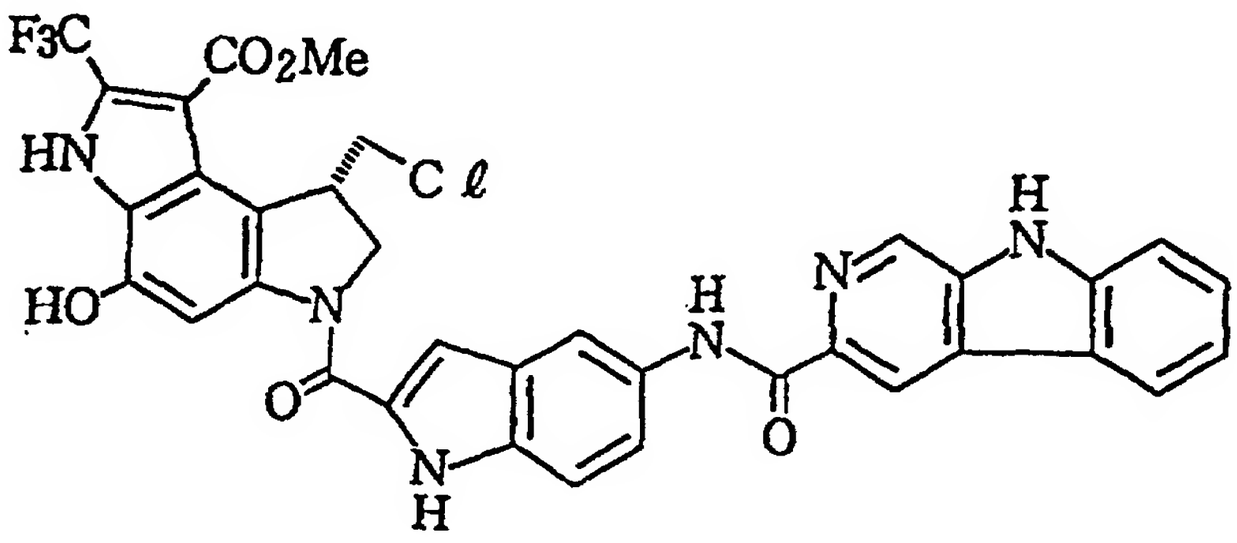


[0146] Methyl (1S)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-[5-[(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 5-(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6.

$[\alpha]_D^{26}$ = +63° (c=0.24, tetrahydrofuran)

(EXAMPLE 62)

[0147]

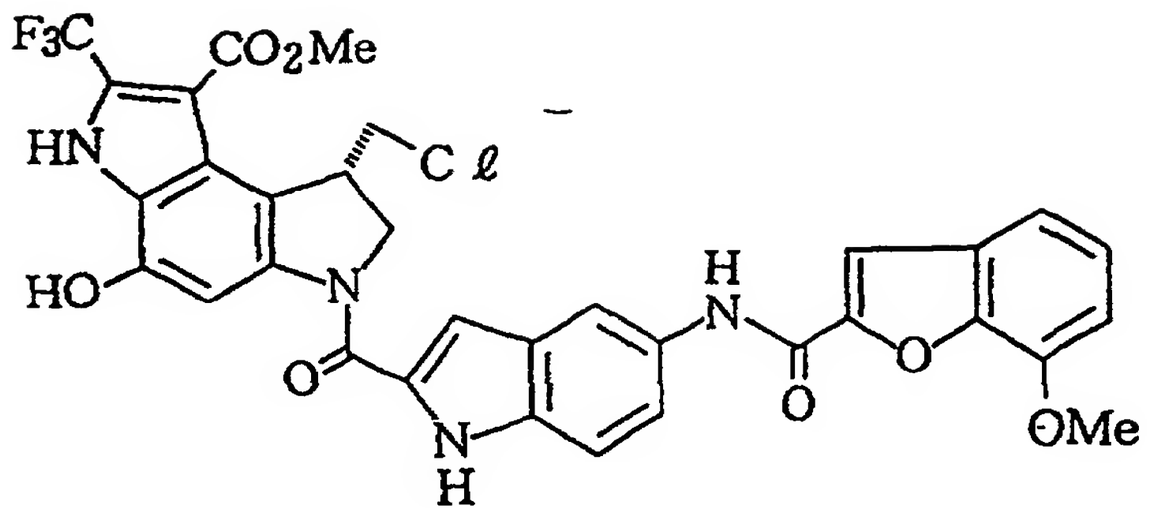


[0148] Methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-[(9H-pyrido[3,4-b]indol-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 5-(9H-pyrido[3,4-b]indol-3-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6.

$[\alpha]_D^{26}$ = +67° (c=0.31, tetrahydrofuran)

(EXAMPLE 63)

[0149]

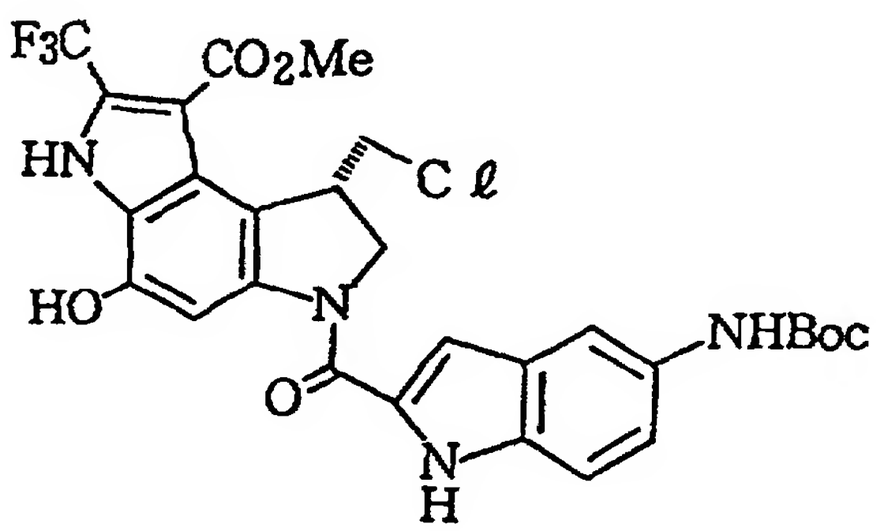


[0150] Methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6.

$[\alpha]_D^{26}$ = +53° (c=0.36, tetrahydrofuran)

(EXAMPLE 64)

[0151]



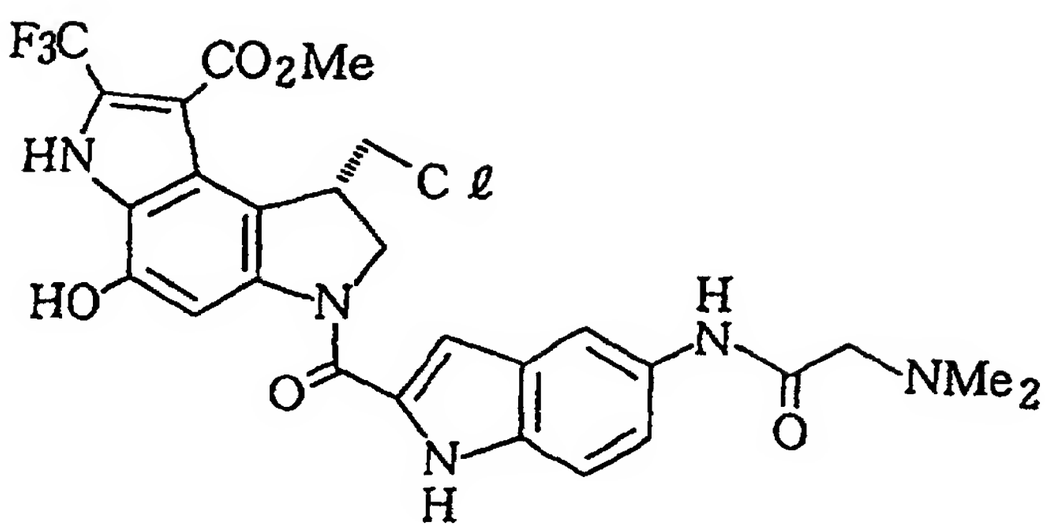
[0152] Methyl (1S)-3-[5-(t-butoxycarbonyl)amino-1H-indol-2-ylcarbonyl]-1-chloromethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 13.8 mg (50 μmol) of 5-(t-butoxycarbonyl)-amino-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 22.4 mg (74 %).

NMR ($CDCl_3$) δ : 1. 55(9H, s),3. 29(1H, t, J=10Hz),3. 77(1H, d, J=10Hz), 3. 92(3H, s),4. 41(1H, m),4. 52(1H, t, J=10Hz),4. 64(1H, d, J=11Hz),6. 57(1H, s), 6.93 (1H, s),7. 01(1H, brd, J=7Hz),7. 21(1H, brd, J=8Hz),7. 66(1H, brs),8. 21(1H, brs), 9. 60(2H, br), 10.13(1H, brs)

$[\alpha]_D^{24}$ = +29° (c=0.20, tetrahydrofuran)

(EXAMPLE 65)

[0153]

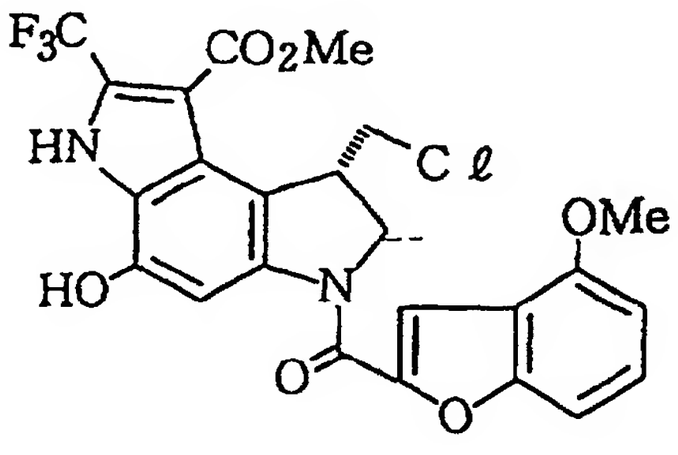


[0154] Methyl (1S)-1-chloromethyl-3-[5-(dimethylaminomethylcarbonyl)amino-1H-indol-2-ylcarbonyl]-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared from 12.1 mg (20 μmol) of methyl (1S)-3-[5-(t-butoxycarbonyl)amino-1H-indol-2-ylcarbonyl]-1-chloromethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate and 2.8 mg (20 μmol) of N,N-dimethylglycine hydrochloride in the same manner as in Example 6 in a yield of 7.8 mg (66 %). NMR (DMSO d_6) δ : 2. 34(6H, s), 3. 12(2H, s), 3. 49(1H, t, J=11Hz), 3. 84 (1H, m), 3. 88(3H, s), 4. 28(1H, m), 4. 53(1H, d, J=11Hz), 4. 68(1H, t, J=9Hz), 7. 10(1H, m), 7. 41(2H, m), 7.93(1H, brs), 8. 08(1H, s),9.62(1H, s), 10.50(1H, br), 11. 64(1H, s), 13. 00 (1H, br)

$[\alpha]_D^{24}$ = +85° (c=0.20, tetrahydrofuran)

(EXAMPLE 66)

[0155]



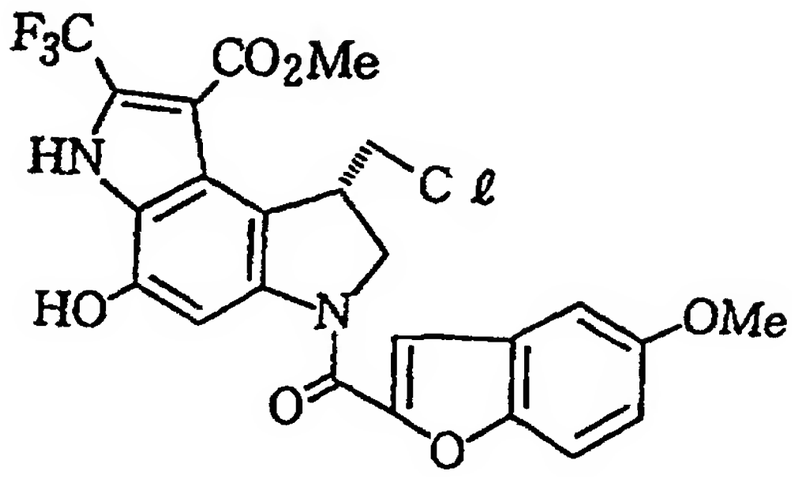
[0156] Methyl (1S)-1-chloromethyl-5-hydroxy-3-(4-methoxybenzofuran-2-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 4.8 mg (25 μmol) of 4-methoxybenzofuran-2-carboxylic acid in the same manner as in Example 6 in a yield of 11.6 mg (89 %).

NMR (DMSOd_6) δ: 3. 52(1H, dd, J=9Hz, J=10Hz), 3. 84(1H, dd, J=3Hz, 11Hz), 3. 87(3H, s), 3. 97(3H, s), 4. 22∼4. 32(1H, m), 4. 49(1H, d, J=11Hz), 4. 69(1H, t, J=10Hz), 6. 89(1H, d, J=8Hz), 7. 31(1H, d, J=9Hz), 7. 45(1H, t, J=8Hz), 7. 62(1H, s), 7. 90(1H, brs), 10. 65(1H, brs), 13. 15(1H, brs)

$[\alpha]_D^{26}$ = -11° (c=0.20, tetrahydrofuran)

(EXAMPLE 67)

[0157]



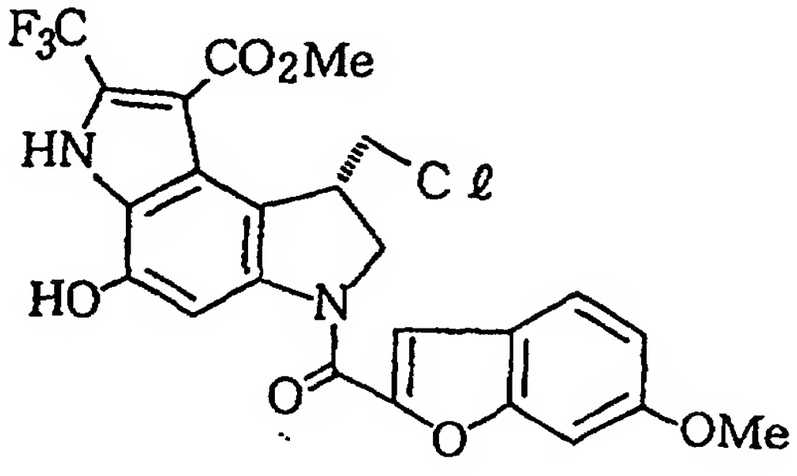
[0158] Methyl (1S)-1-chloromethyl-5-hydroxy-3-(5-methoxybenzofuran-2-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 4.8 mg (25 μmol) of 5-methoxybenzofuran-2-carboxylic acid in the same manner as in Example 6 in a yield of 7.1 mg (54 %).

NMR (DMSO d_6) δ : 3. 53(1H, dd, J=8Hz, J=10Hz), 3. 83(3H, s), 3. 82~3. 90(1H, m), 3. 87(3H, s), 4. 24~4. 32 (1H, m), 4. 52(1H, d, J=12Hz), 4. 65(1H, t, J=10Hz), 7. 09(1H, dd, J=3Hz, J=9Hz), 7. 29(1H, d, J=3Hz), 7. 61(1H, s), 7. 63(1H, d, J=9Hz), 7.91 (1H, brs), 10. 60(1H, brs), 13. 11(1H, brs)

$[\alpha]_D^{26}$ = +1.4° (c=0.20, tetrahydrofuran)

(EXAMPLE 68)

[0159]



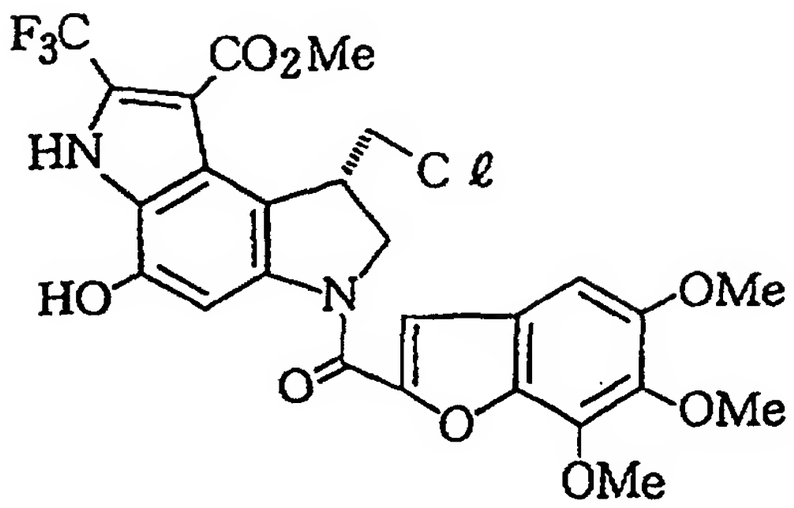
[0160] Methyl (1S)-1-chloromethyl-5-hydroxy-3-(6-methoxybenzofuran-2-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 4.8 mg (25 μmol) of 6-methoxybenzofuran-2-carboxylic acid in the same manner as in Example 6 in a yield of 9.8 mg (75 %).

NMR (DMSO d_6) δ : 3. 52(1H, dd, J=9Hz, J=11Hz), 3. 87(3H, s), 3. 88(3H, s), 4. 24~4. 32(1H, m), 4. 53(1H, d, J=11Hz), 4. 65(1H, dd, J=9Hz, J=11Hz), 7. 00(1H, dd, J=2Hz, J=9Hz), 7. 32(1H, d, J=2Hz), 7. 63(1H, s), 7. 68(1H, d, J=9Hz), 7. 90(1H, brs), 10. 59(1H, brs), 13. 09(1H, brs)

$[\alpha]_D^{26}$ = +16° (c=0.20, tetrahydrofuran)

(EXAMPLE 69)

[0161]



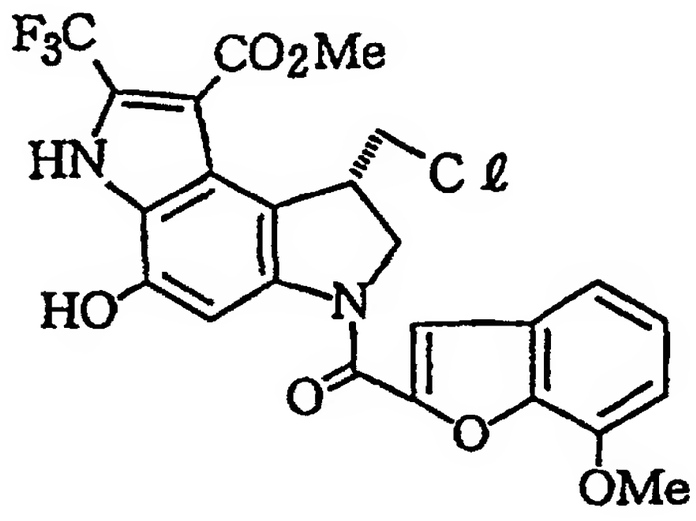
[0162] Methyl (1S)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-(5,6,7-trimethoxybenzofuran-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 6.3 mg (25 μmol) of 5,6,7-trimethoxybenzofuran-2-carboxylic acid in the same manner as in Example 6 in a yield of 10.5 mg (72 %).

NMR ($CDCl_3$) δ : 3. 36(1H, t, J=11Hz), 3. 85~3. 95(1H, m), 3. 91(3H, s), 3. 95(3H, s), 3. 97(3H, s), 4. 28(3H, s), 4. 46~4. 51(1H, m), 4. 65(1H, dd, J=9Hz, J= 11Hz), 4. 90(1H, t, J=11Hz), 6. 83(1H, s), 7. 68(1H, s), 8. 54(1H, s), 9. 72(1H, brs), 11. 17(1H, brs)

$[\alpha]_D^{23}$ = +18° (c=0.20, tetrahydrofuran)

(EXAMPLE 70)

[0163]



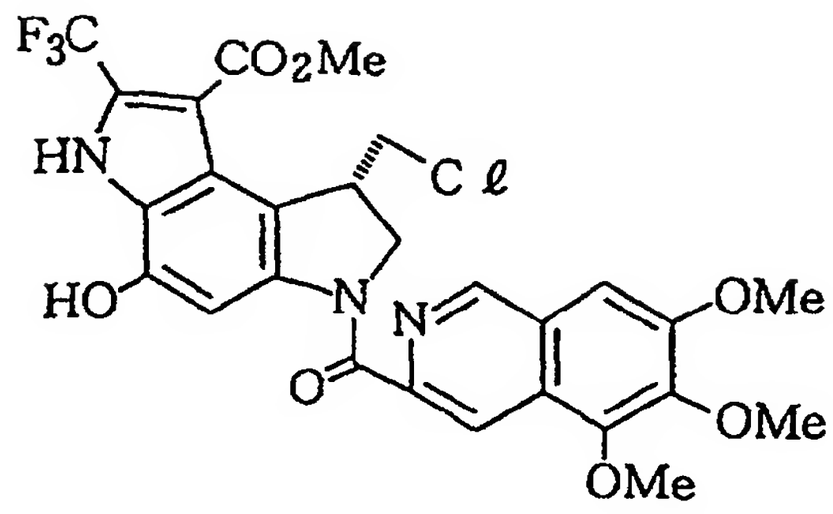
[0164] Methyl (1S)-1-chloromethyl-5-hydroxy-3-(7-methoxybenzofuran-2-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 4.4 mg (23 μmol) of 7-methoxybenzofuran-2-carboxylic acid in the same manner as in Example 6 in a yield of 9.3 mg (77 %).

NMR ($DMSOd_6$) δ : 3. 52(1H, dd, J=8Hz, J=10Hz), 3. 84(1H, dd, J=3Hz, J= 10Hz), 3. 88(3H, s), 4. 00(3H, s), 4. 29(1H, m), 4. 52(1H, d, J=10Hz), 4. 64(1H, dd, J=8Hz, J=10Hz), 7. 09(1H, d, J=8Hz), 7. 28(1H, t, J=8Hz), 7. 36(1H, dd, J=1Hz, J=8Hz), 7. 66(1H, s), 7. 92(1H, brs), 10.59(1H, brs), 13. 09(1H, brs)

$[\alpha]_D^{24}$ = +33° (c=0.20, tetrahydrofuran)

(EXAMPLE 71)

[0165]



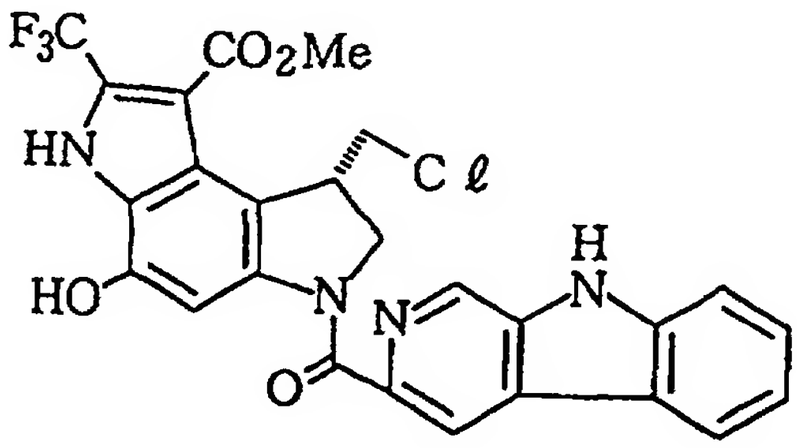
[0166] Methyl (1S)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 6.0 mg (23 μmol) of 5,6,7-trimethoxyisoquinoline-3-carboxylic acid in the same manner as in Example 6 in a yield of 11.1 mg (81 %).

NMR (DMSOd_6) δ : 3. 44 (1H, t, J=9Hz), 3. 79(1H, m), 3. 85(3H, s), 3. 95 (3H, s), 4. 01(3H, s), 4. 04(3H, s), 4. 16 (1H, m), 4. 21(1H, d, J=11Hz), 4. 48(1H, t, J= 9Hz), 7. 50(1H, s), 7. 96(1H, brs), 8. 26(1H, s), 9. 21(1H, s), 10. 60 (1H, br), 12. 90(1H, br)

$[\alpha]_D^{24}$ = -46° (c=0.20, tetrahydrofuran)

EXAMPLE 72)

[0167]



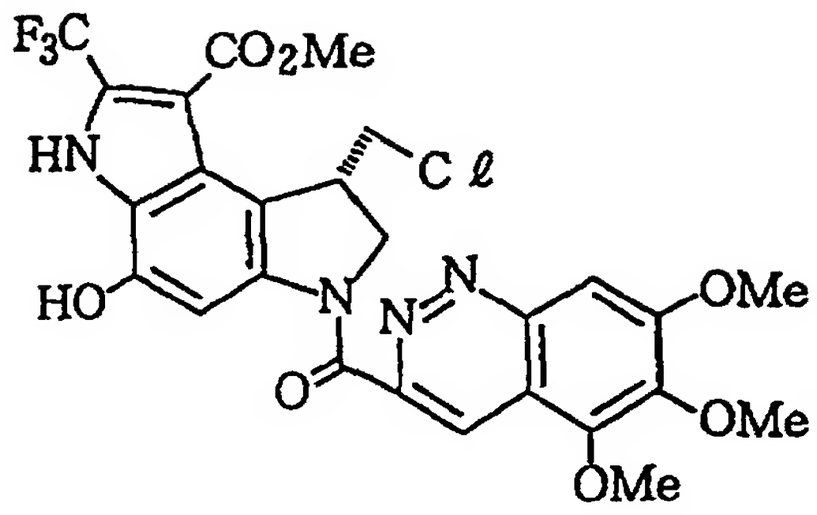
[0168] Methyl (1S)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-(9H-pyrido[3,4-b]indol-3-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 4.9 mg (23 μmol) of 9H-pyrido[3,4-b]indole-3-carboxylic acid in the same manner as in Example 6 in a yield of 9.9 mg (79 %).

NMR (DMSO d_6) δ :3.42(1H, t, J=9Hz),3.81(1H, m),3.85(3H, s),4.16 (1H, m), 4.30(1H, d, J=11Hz), 4.55(1H, m), 7.31(1H, t, J=8Hz),7.60(1H, t, J=8Hz), 7. 67(1H, d, J=8Hz),7.98(1H, brs),8.37(1H, d, J=8Hz),8.67(1H, brs),8.95(1H, s), 10. 58(1H, br),11.95(1H, s),13.00(1H, br)

$[\alpha]_D^{24}$ = -52° (c=0.20, tetrahydrofuran)

(EXAMPLE 73)

[0169]



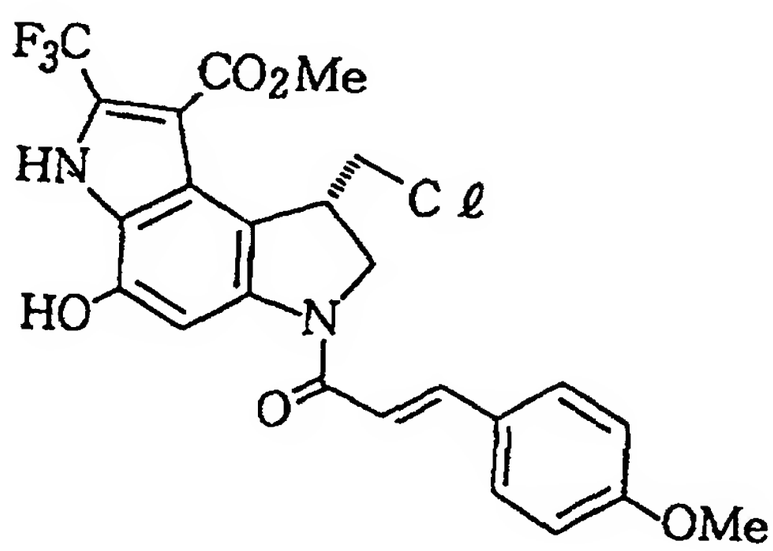
[0170] Methyl (1S)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-(5,6,7-trimethoxycinnolin-3-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 6.1 mg (23 μmol) of 5,6,7-trimethoxycinnoline-3-carboxylic acid in the same manner as in Example 6 in a yield of 9.9 mg (72 %).

NMR (DMSOd$_6$) δ : 3. 50(1H, t, J=10Hz), 3. 80(1H, dd, J=2Hz, J=10Hz), 3. 86(3H, s), 4. 00(3H, s), 4. 08(3H, s), 4. 11(3H, s), 4. 18∼4. 24(2H, m), 4. 54(1H, dd, J= 9Hz, J=11Hz), 7. 75(1H, s), 8. 04(1H, s), 8. 45(1H, s), 10. 63(1H, s), 13. 10(1H, s)

$[\alpha]_D^{24}$ = -19° (c=0.20, tetrahydrofuran)

(EXAMPLE 74)

[0171]



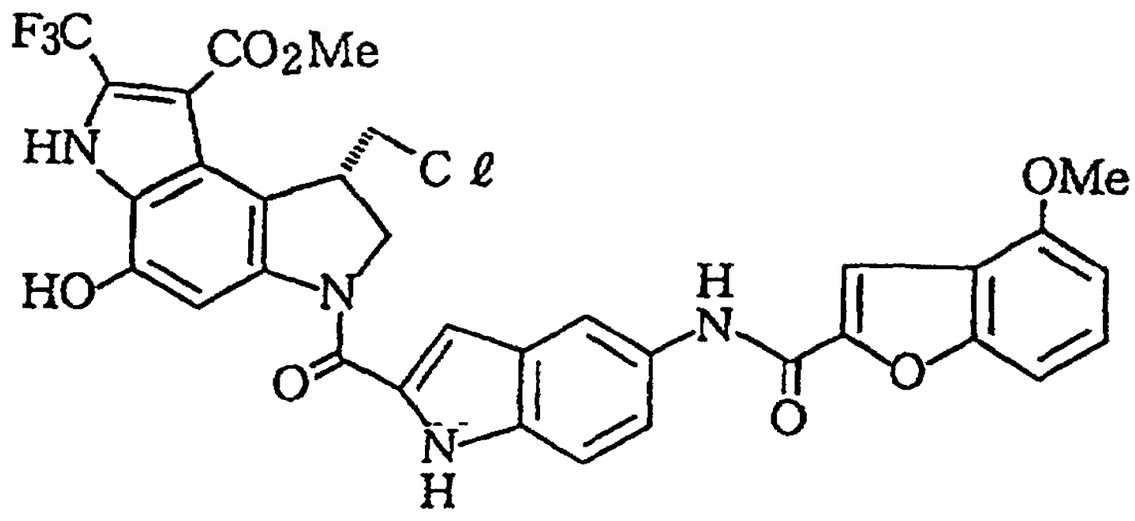
[0172] Methyl (1S)-1-chloromethyl-5-hydroxy-3-[2-(4-methoxyphenyl)ethylene-1-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 4.1 mg (23 μmol) of 4-methoxycinnamic acid in the same manner as in Example 6 in a yield of 6.1 mg (52 %).

NMR (DMSO d$_6$) δ : 3. 46(1H, dd, J=9Hz, J=10Hz),3. 79∼3. 82(1H, m), 3. 82(3H, s),3. 88(3H, s),4. 26(1H, br), 4. 37(1H, t, J=10Hz),4. 43(1H, d, J=10Hz),6. 99 (2H, d, J=9Hz),7.05(1H, d, J=15Hz),7. 62(1H, d, J=15Hz),7. 74(2H, d, J=9Hz),8. 10(1H, brs), 10. 49(1H, s),13. 00(1H, s)

$[\alpha]_D^{24}$ = -59° (c=0.20, tetrahydrofuran)

(EXAMPLE 75)

[0173]



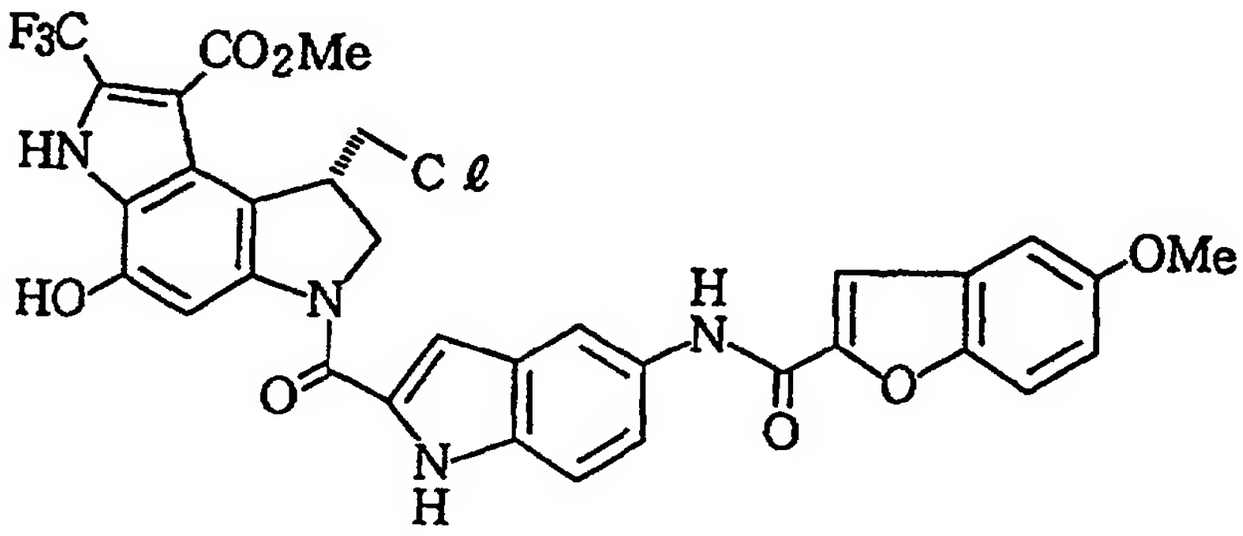
[0174] Methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(4-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 8.8 mg (25 μmol) of 5-(4-methoxybenzofuran-2-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 12.5 mg (73 %).

NMR (DMSO d_6) δ : 3. 53(1H, dd, J=9Hz, J=11Hz), 3. 82~3. 92(1H, m), 3. 88(3H, s), 3. 97(3H, s), 4.25~4.35 (1H, m), 4. 54(1H, d, J=11Hz), 4. 72(1H, t, J=11Hz), 6. 89(1H, d, J=8Hz), 7. 18(1H, s), 7. 31(1H, d, J=9Hz), 7. 44(1H, t, J=8Hz), 7. 49(1H, d, J=9Hz), 7. 58~7. 64(1H, m), 7. 79(1H, s), 7. 95(1H, brs), 8. 21(1H, s), 10. 39(1H, s), 10. 59(1H, brs), 11. 74(1H, s), 13. 10(1H, brs)

$[\alpha]_D^{25}$ = +57° (c=0.20, tetrahydrofuran)

(EXAMPLE 76)

[0175]



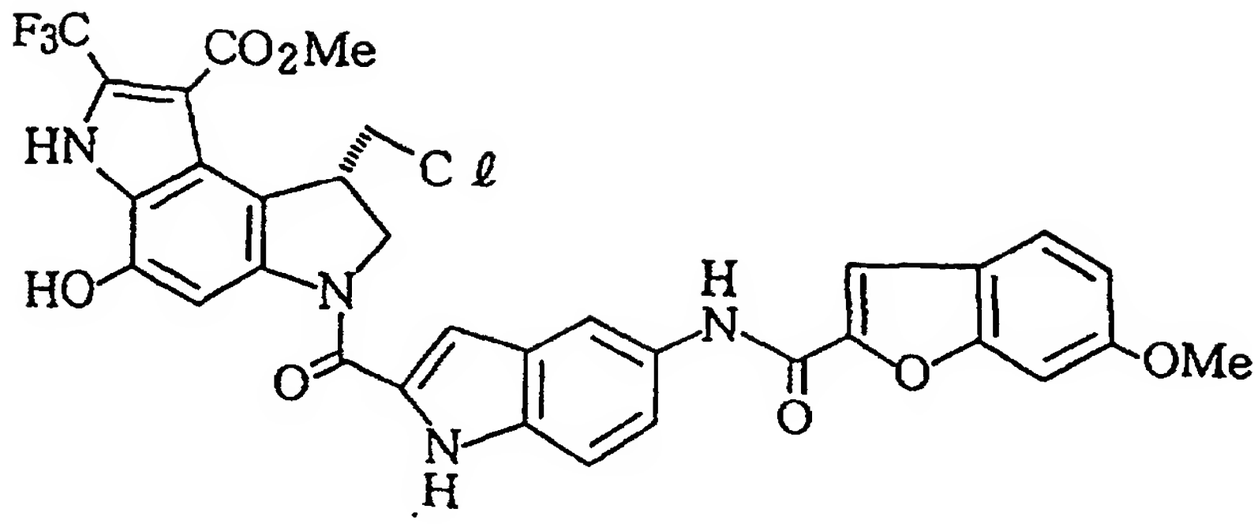
[0176] Methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(5-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 8.8 mg (25 μmol) of 5-(5-methoxybenzofuran-2-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 10.7 mg (63 %).

NMR (DMSOd_6) δ : 3. 46(1H, dd, J=8Hz, J=11Hz), 3. 77(3H, s), 3. 78~3, 84(1H, m), 3. 81(3H, s), 4. 18~4. 26 (1H, m), 4. 47(1H, d, J=11Hz), 4. 65(1H, t, J=11Hz), 7. 02(1H, dd, J=2Hz, J=9Hz), 7. 11(1H, s), 7. 25(1H, d, J=3Hz), 7. 42(1H, d, J=9Hz), 7. 53 ~7. 57(2H, m), 7. 62(1H, s), 7. 89(1H, brs), 8. 14(1H, s), 10. 38(1H, s), 10. 53(1H, s), 10. 53(1H, s), 11. 67(1H, s), 13. 04(1H, s)

$[\alpha]_D^{25}$ = +44° (c=0.20, tetrahydrofuran)

(EXAMPLE 77)

[0177]



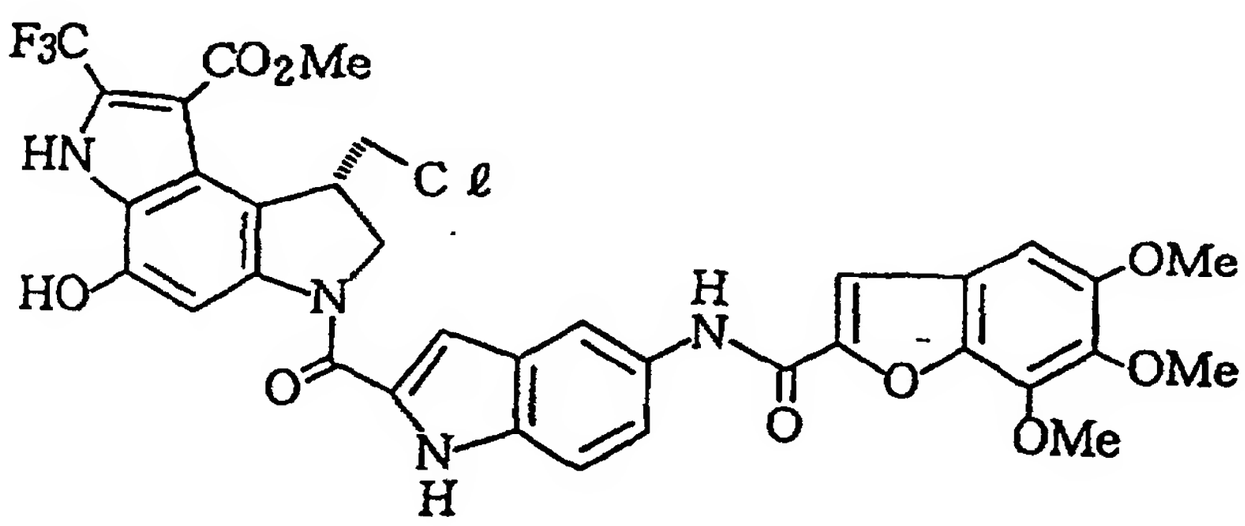
[0178] Methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(6-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 8.8 mg (25 μmol) of 5-(6-methoxybenzofuran-2-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 13.7 mg (80 %).

NMR (DMSOd_6) δ : 3.53 (1H,dd,J = 10Hz,J = 11Hz), 3. 82~3. 92(1H, m), 3. 87(3H, s), 3. 89(3H, s), 4. 25~4. 28 (1H, m), 4. 54(1H, d, J=10Hz), 4. 70~4. 75(1H, m), 7. 00(1H, dd, J=2Hz, J=9Hz), 7. 18(1H, s), 7. 28(1H, d, J=2Hz), 7. 49(1H, d, J=9Hz), 7. 60(1H, dd, J=2Hz, J=9Hz), 7. 66~7. 74(2H, m), 7. 95(1H, brs), 8. 20(1H, s), 10. 34(1H, s), 10. 59(1H, s), 11. 73(1H, s), 13. 11(1H, s)

$[\alpha]_D^{26}$ = +42° (c=0.20, tetrahydrofuran)

(EXAMPLE 78)

[0179]



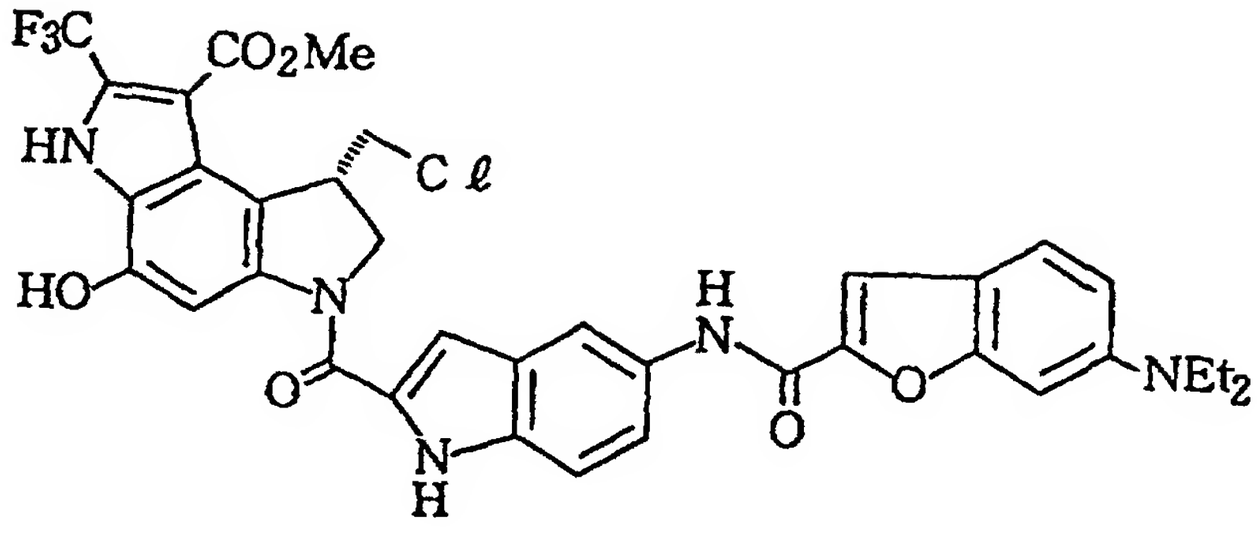
[0180] Methyl (1S)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-[5-(5,6,7-trimethoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 8.2 mg (20 μmol) of 5-(5,6,7-trimethoxybenzofuran-2-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 8.7 mg (59 %).

NMR (DMSOd_6) δ : 3. 53(1H, dd, J=9Hz, J=11Hz), 3. 81 (3H, s), 3. 82~3. 92(1H, m), 3. 86(3H, s), 3. 88(3H, s), 4. 17(3H, s), 4. 25~4. 35(1H, m), 4. 54(1H, d, J= 11Hz), 4. 72(1H, t, J=11Hz), 7. 08(1H, s), 7. 18(1H, s), 7. 49(1H, d, J=9Hz), 7.56(1H, J =2Hz, J=9Hz), 7. 69(1H, s), 7. 95(1H, brs), 8. 17(1H, s),10. 32(1H, s), 10. 60(1H, brs), 11. 75(1H, s), 13. 10(1H, brs)

$[\alpha]_D^{25}$ = +55° (c=0.20, tetrahydrofuran)

(EXAMPLE 79)

[0181]



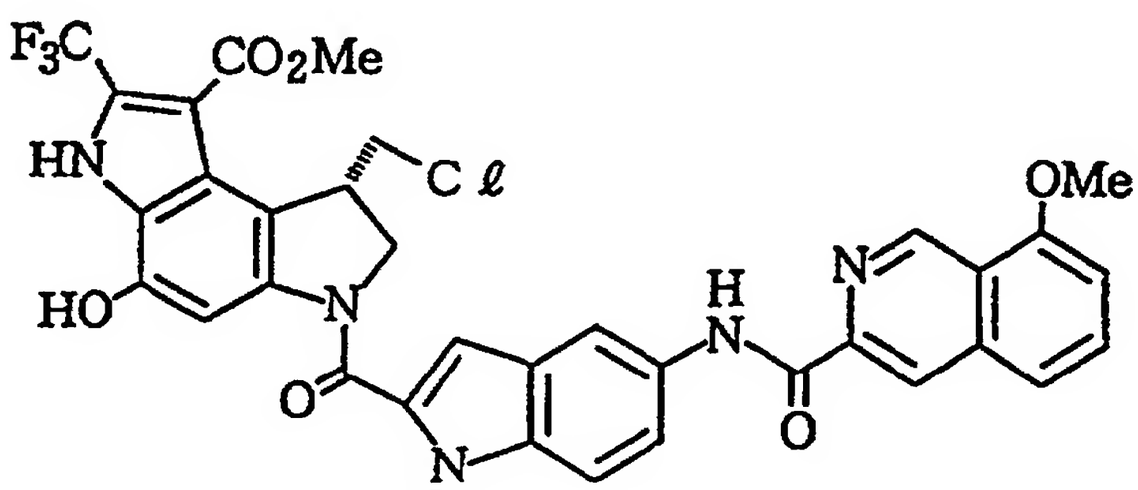
[0182] Methyl (1S)-1-chloromethyl-3-[5-(6-diethylaminobenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 9.8 mg (25 μmol) of 5-(6-diethylaminobenzofuran-2-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 15.1 mg (83 %).

NMR (DMSO d_6) δ : 1. 15(6H, t, J=7Hz), 3. 43(4H, q, J=7Hz), 3. 50~3. 55 (1H, m), 3. 85~3. 85(1H, m), 3. 88 (3H, s), 4. 25~4. 35(1H, m), 4. 53(1H, d, J=11Hz), 4. 70~4. 78(1H, m), 6. 79(1H, s), 6. 81(1H, s), 7. 17(1H, s), 7. 47 (1H, d, J=9Hz), 7. 52~7. 61(3H, m), 7. 95(1H, brs), 8. 19(1H, s), 10. 14(1H, s), 10. 59(1H, brs), 11. 70(1H, s), 13. 11 (1H, brs)

$[\alpha]_D^{25}$ = +58° (c=0.20, tetrahydrofuran)

(EXAMPLE 80)

[0183]



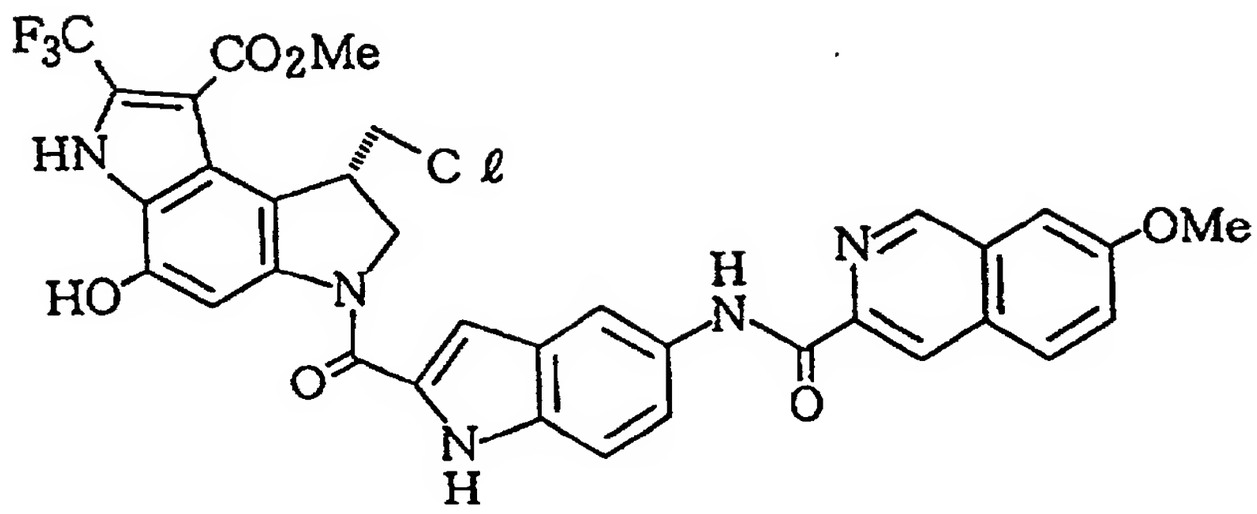
[0184] Methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(8-methoxyisoquinolin-3-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 4.0 mg (11 μmol) of 5-(8-methoxyisoquinolin-3-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 4.0 mg (52 %).

NMR (DMSO d_6) δ : 3. 52(1H, t, J=10Hz), 3. 82~3. 95(1H, m), 3. 88(3H, s), 4. 08(3H, s), 4. 25~4. 35(1H, m), 4. 54(1H, d, J=11Hz), 4. 71(1H, t, J=10Hz), 7. 18(1H, s), 7. 28(1H, d, J=8Hz), 7. 50(1H, d, J=9Hz), 7. 70~7. 75(1H, m), 7. 78(1H, d, J=8Hz), 7. 83(1H, t, J=8Hz), 7. 95(1H, brs), 8. 38(1H, brs), 8. 66(1H, s), 9.60(1H, s), 10. 60(1H, brs), 10. 70(1H, s), 11. 72(1H, s), 13. 10(1H, brs)

$[\alpha]_D^{25}$ = +53° (c=0.20, tetrahydrofuran)

(EXAMPLE 81)

[0185]



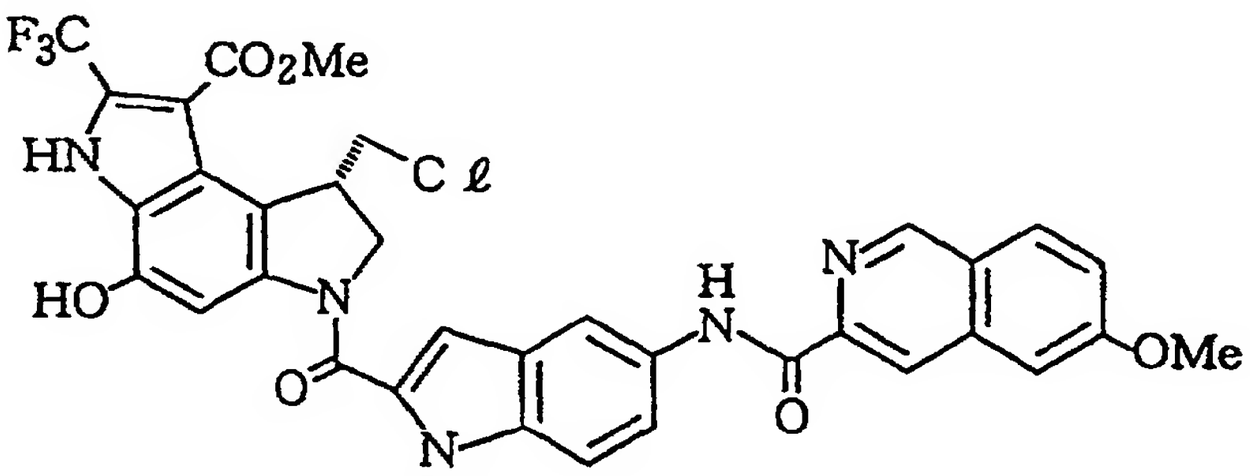
[0186] Methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(7-methoxyisoquinolin-3-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 7.3 mg (20 μmol) of 5-(7-methoxyisoquinolin-3-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 9.4 mg (68 %).

NMR (DMSO d_6) δ: 3. 52(1H, dd, J=8Hz, J=10Hz), 3. 83~3. 93(1H, m), 3. 88(3H, s), 3. 98(3H, s), 4. 25~4. 35 (1H, m), 4. 54(1H, d, J=10Hz), 4. 73(1H, t, J=10Hz), 7. 18(1H, s), 7. 49(1H, d, J=9Hz), 7. 55(1H, dd, J=3Hz, J=9Hz), 7. 68~7. 76(2H, m), 7. 95 (1H, brs), 8. 18(1H, d, J=9Hz), 8. 37(1H, d, J=2Hz), 8. 65(1H, s), 9. 37(1H, s), 10. 59(1H, s), 10. 62(1H, s), 11. 71(1H, s), 13. 10(1H, brs)

$[\alpha]_D^{25}$ = +71° (c=0. 20, tetrahydrofuran)

(EXAMPLE 82)

[0187]



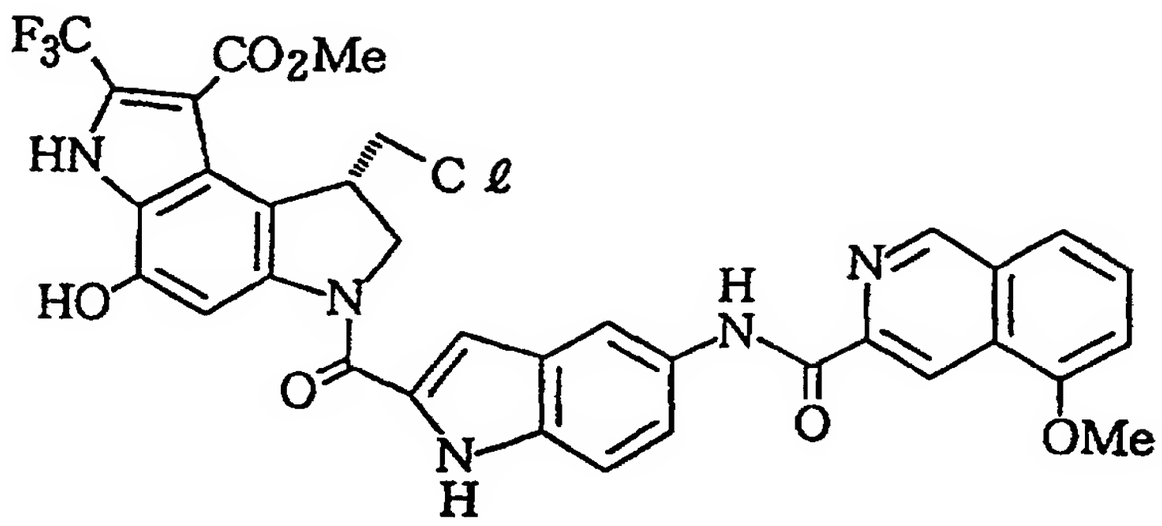
[0188] Methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(6-methoxyisoquinolin-3-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 9.0 mg (25 μmol) of 5-(6-methoxyisoquinolin-3-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 13.6 mg (78 %).

NMR (DMSOd_6) δ : 3. 53(1H,dd,J=9Hz,J=11Hz), 3. 84~3. 94(1H, m), 3. 89(3H, s), 3. 97(3H, s), 4. 25~4. 35(1H, m), 4. 54(1H, d, J=11Hz), 4. 73(1H, t, J=11Hz), 7. 18(1H, s), 7. 45(1H, dd, J=3Hz, J=9Hz), 7. 49(1H, d, J=9Hz), 7. 67 (1H, d, J=2Hz), 7. 70 ~7. 76(1H, m), 7. 95(1H, brs), 8. 20(1H, d, J=9Hz), 8. 38(1H, s), 8. 61(1H, s), 9. 32(1H, s), 10. 59(1H, s), 10. 66(1H, s), 11. 72(1H, s), 13. 11(1H, s)

$[\alpha]_D^{25}$ = +60° (c=0.20, tetrahydrofuran)

(EXAMPLE 83)

[0189]



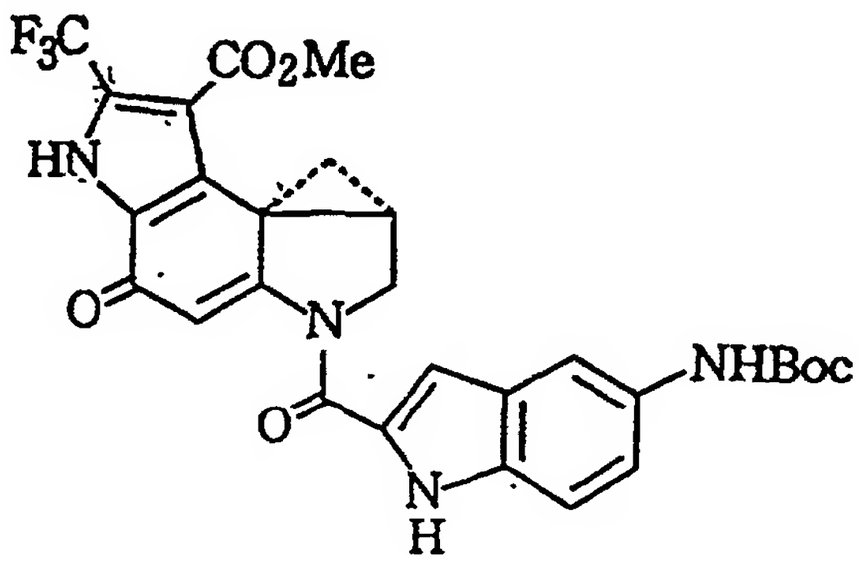
[0190] Methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(5-methoxyisoquinolin-3-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 9.0 mg (25 μmol) of 5-(5-methoxyisoquinolin-3-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 11.1 mg (64 %).

NMR ($DMSOd_6$) δ : 3. 53(1H, t, J=11Hz), 3. 84~3. 95(1H, m), 3. 88(3H, s), 4. 08(3H, s), 4. 25~4. 35(1H, m), 4. 54(1H, d, J=11Hz), 4. 73(1H, t, J=11Hz), 7. 19(1H, s), 7. 37(1H, d, J=8Hz), 7. 50(1H, d, 3=9Hz), 7. 73(1H, dd, J=2Hz, J=9Hz), 7. 78(1H, t, J =8Hz), 7. 85(1H, d, J=8Hz), 7. 95(1H, brs), 8. 38(1H, d, J=2Hz), 8.83(1H, s), 9.44(1H, s), 10. 60 (1H, brs), 10. 68(1H, s), 11. 72(1H, s), 13. 10(1H, brs)

$[\alpha]_D^{25}$ = +66° (c=0.20, tetrahydrofuran)

(EXAMPLE 84)

[0191]



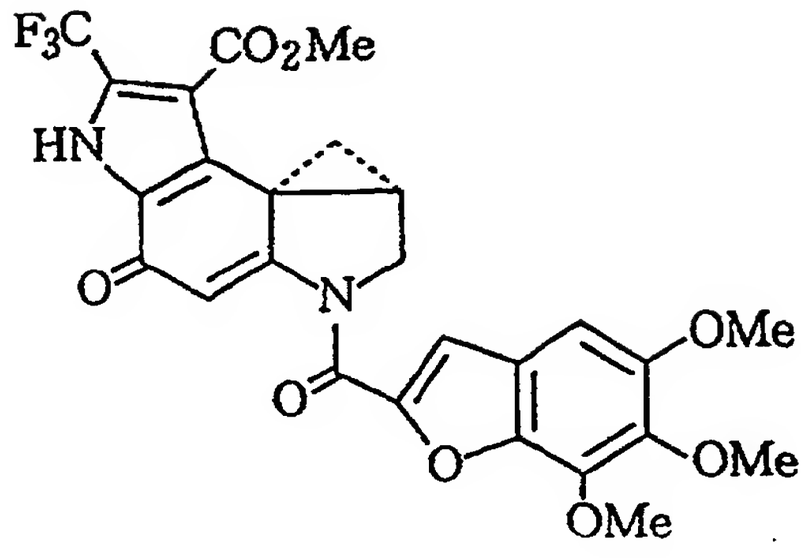
[0192] Methyl (7bR,8aS)-2-[5-(t-butoxycarbonyl)amino-1H-indole-2-ylcarbonyl]-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indole-4(5H)-one-7-carboxylate was prepared by using 5.5 mg (9.1 μmol) of methyl (1S)-3-[5-(t-butoxycarbonyl)amino-1H-indol-2-ylcarbonyl]-1-chloromethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 20 in a yield of 4.9 mg (95 %).

NMR ($CDCl_3$) δ : 1. 40(1H, t, J=4Hz), 1. 54(9H, s), 2. 34(1H, dd, J=4Hz, J =8Hz), 3. 66(1H, m), 3. 87(3H, s), 4.48(2H, m), 6.85(1H, brs), 6. 96(1H, d, J=1Hz), 7. 18 (1H, s), 7. 22(1H, dd, J=2Hz, J=9Hz), 7. 38(1H, d, J=9Hz), 7. 82(1H, brs), 9. 98 (1H, s), 11. 83 (1H, br)

$[\alpha]_D^{24}$ = +120° (c=0.20, tetrahydrofuran)

(EXAMPLE 85)

[0193]



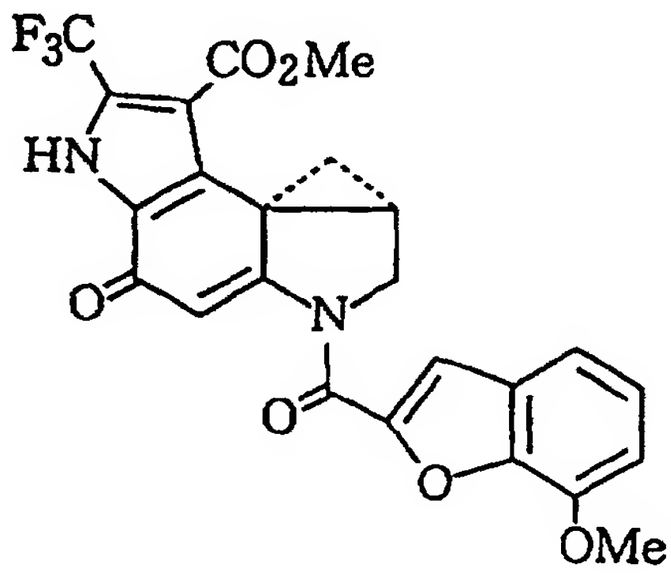
[0194] Methyl (7bR,8aS)-5-trifluoromethyl-2-(5,6,7-trimethoxybenzofuran-2-ylcarbonyl)-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate was prepared by using 20.1 mg (35 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-(5,6,7-trimethoxybenzofuran-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 20 in a yield of 14.1 mg (74 %).

NMR ($CDCl_3$) δ : 1. 48(1H, t, J=4Hz), 2. 42(1H, dd, J=4Hz, J=8Hz), 3. 88 (3H, s), 3. 92(3H, s), 3. 94(3H, s), 4. 14(3H, s), 4. 44∼4. 53(2H, m), 6. 76(1H, brs), 6. 81(1H, s), 7. 55(1H, s)

$[\alpha]_D^{27}$ = +221° (c=1.1, chloroform)

(EXAMPLE 86)

[0195]



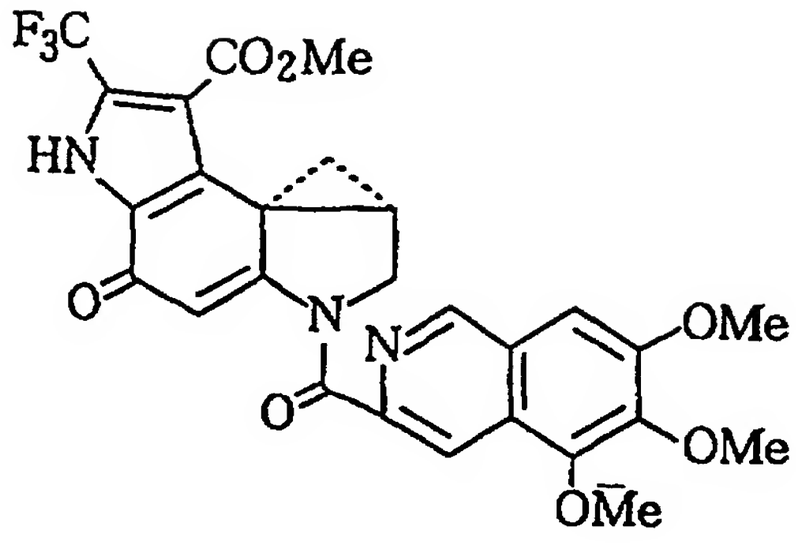
[0196] Methyl (7bR,8aS)-2-(7-methoxybenzofuran-2-ylcarbonyl)-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate was prepared by using 5.7 mg (11 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-(7-methoxybenzofuran-2-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 20 in a yield of 5.3 mg (98 %).

NMR ($CDCl_3$) δ : 1. 46(1H, t, J=4Hz), 2. 39(1H, dd. J=4Hz, J=8Hz),3. 68 (1H, m), 3. 87(3H, s), 4. 00(3H, s), 4. 54∼4. 62(2H, m), 6. 94(1H, dd, J=1H J=7Hz), 7. 00(1H, brs), 7. 24(1H, d, J=8Hz), 7. 28(1H, dd, J=1Hz, J=8Hz), 7. 61 (1H, s),10. 55 (1H, br)

$[\alpha]_D^{24}$ = +201° (c=0. 53, chloroform)

(EXAMPLE 87)

[0197]



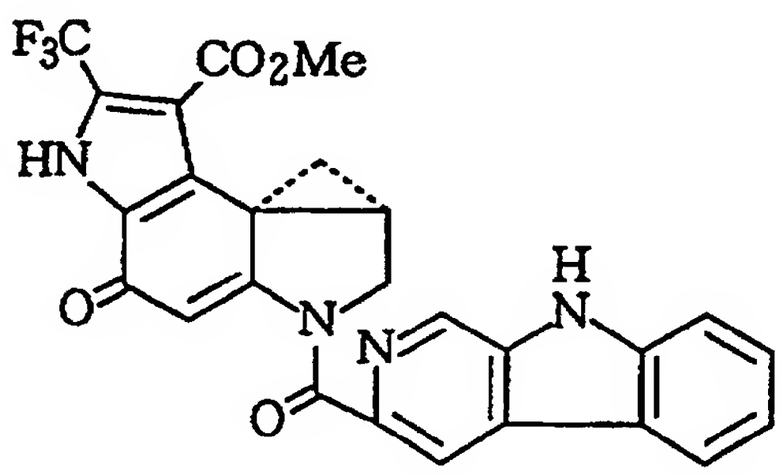
[0198] Methyl (7bR,8aS)-6-trifluoromethyl-2-(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate was prepared by using 5.8 mg (9.7 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 20 in a yield of 5.0 mg (93 %).

NMR ($CDCl_3$) δ : 1. 63(1H, t, J=4Hz), 2. 42(1H, dd, J=4Hz, J=8Hz), 3. 58 (1H, m), 3. 87(3H, s), 4. 03(3H, s), 4. 05(3H, s), 4. 09(3H, s), 4. 30(1H, d, J=12Hz), 4. 45 (1H, dd, J=5Hz, J=12Hz), 6. 25(1H, brs), 7. 08(1H, s), 8. 44(1H, s), 8. 98 (1H, s), 10.42 (1H, br)

$[\alpha]_D^{24}$ = +73° (c=0.50, chloroform)

(EXAMPLE 88)

[0199]



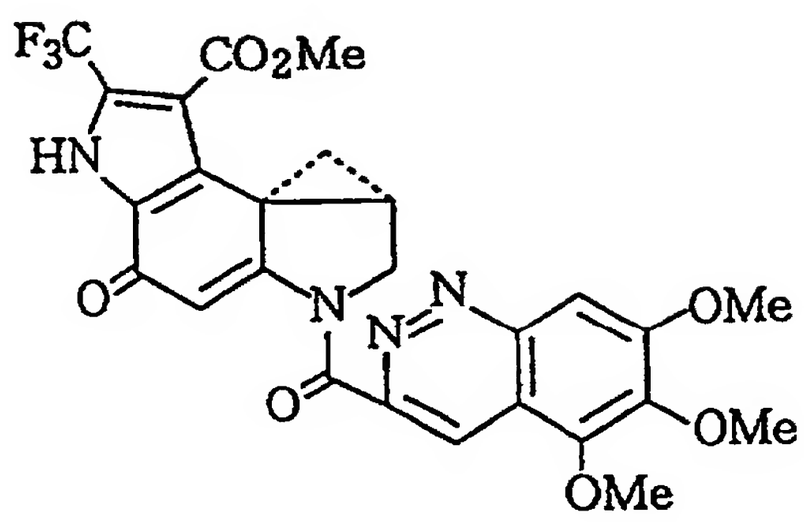
[0200] Methyl (7bR,8aS)-2-(9H-pyrido[3,4-b]indol-3-ylcarbonyl)-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate was prepared by using 6.7 mg (12 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-(9H-pyrido[3,4-b]indol-3-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 20 in a yield of 5.4 mg (88 %).

NMR ($CDCl_3$) δ : 1. 56(1H, brs), 2. 27(1H, brd, J=4Hz), 3. 55(1H, m), 3. 83 (3H, s), 4. 21(1H, d, J=10Hz), 4. 40 (1H, dd, J=4Hz, J=11Hz), 6. 06(1H, brs), 7. 33(1H, t, J=8Hz), 7. 50(1H, d, J=8Hz), 7. 58(1H, t, J=8Hz), 8. 06(1H, d, J=8Hz), 8. 46(1H, s),8. 84 (1H, brs), 9. 83(1H, br),10. 62(1H, br)

$[\alpha]_D^{24}$ = +81° (c=0.54, chloroform)

(EXAMPLE 89)

[0201]



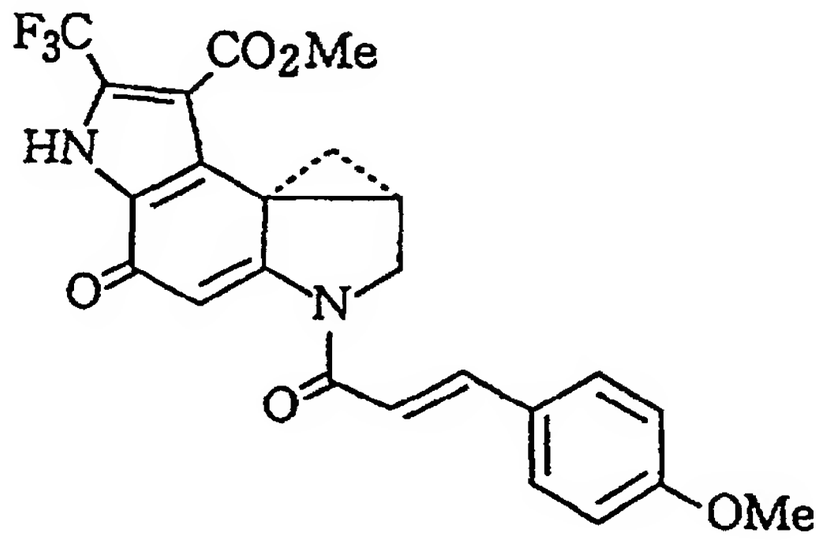
[0202] Methyl (7bR, 8aS) -6-trifluoromethyl-2-(5,6,7-trimethoxycinnolin-3-ylcarbonyl)-1,2,8,8a-tatrahydrocyclopropa [c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate was prepared by using 5.7 mg (9.6 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-(5,6,7-trimethoxycinnolin-3-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 20 in a yield of 4.6 mg (85 %).

NMR ($CDCl_3$) δ : 1. 66(1H, brs), 2. 43(1H, dd, J=4Hz, J=8Hz), 3. 63(1H, m), 3. 87(3H, s), 4. 07(3H, s), 4. 13 (3H×2, s), 4. 45(1H, d, J=11Hz), 4. 60(1H, dd, J=5Hz, J =11Hz), 6. 56(1H, br), 7. 62(1H, s), 8. 59(1H, s), 10. 40(1H, br)

$[\alpha]_D^{24}$ = +141° (c=0.46, chloroform)

(EXAMPLE 90)

[0203]



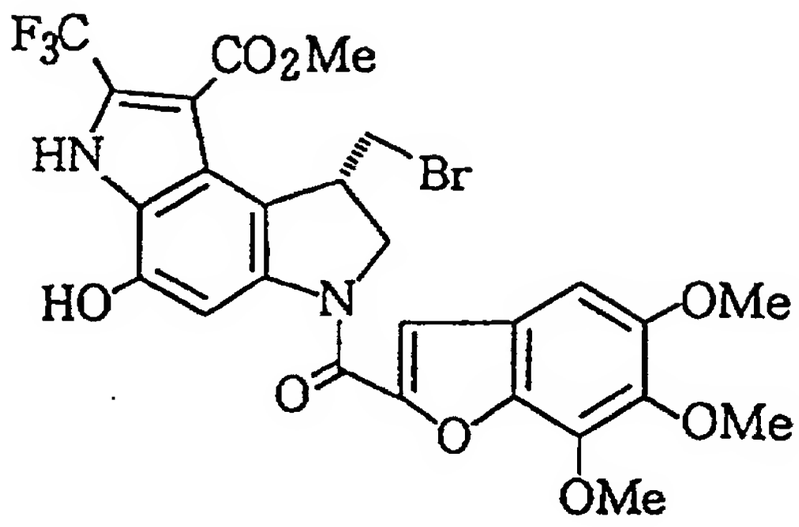
[0204] Methyl (7bR,8aS)-2-[2-(4-methoxyphenyl)ethylene-1-ylcarbonyl)-6-trifluoromethyl-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate was prepared by using 3.8 mg (7.4 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-[2-(4-methoxyphenyl)ethylene-1-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e] indole-8-carboxylate in the same manner as in Example 20 in a yield of 3.5 mg (99 %).

NMR ($CDCl_3$) δ : 1. 37(1H,dd,J=4Hz,J=5Hz), 2. 39(1H,dd,J=4Hz,J=8Hz), 3. 59(1H, m), 3. 86(3H, s), 3. 87(3H, s), 4. 18(1H, dd, J=5Hz, J=11Hz), 4. 25(1H, d, J= 11Hz), 6. 72(1H, d, J=16Hz), 6. 78(1H, br), 6. 93(2H, d, J=9Hz), 7. 53(2H, d, J=9Hz), 7. 80(1H, d, J=15Hz), 10. 41(1H, br)

$[\alpha]_D^{24}$ = +129° (c=0.35, chloroform)

(EXAMPLE 91)

[0205]



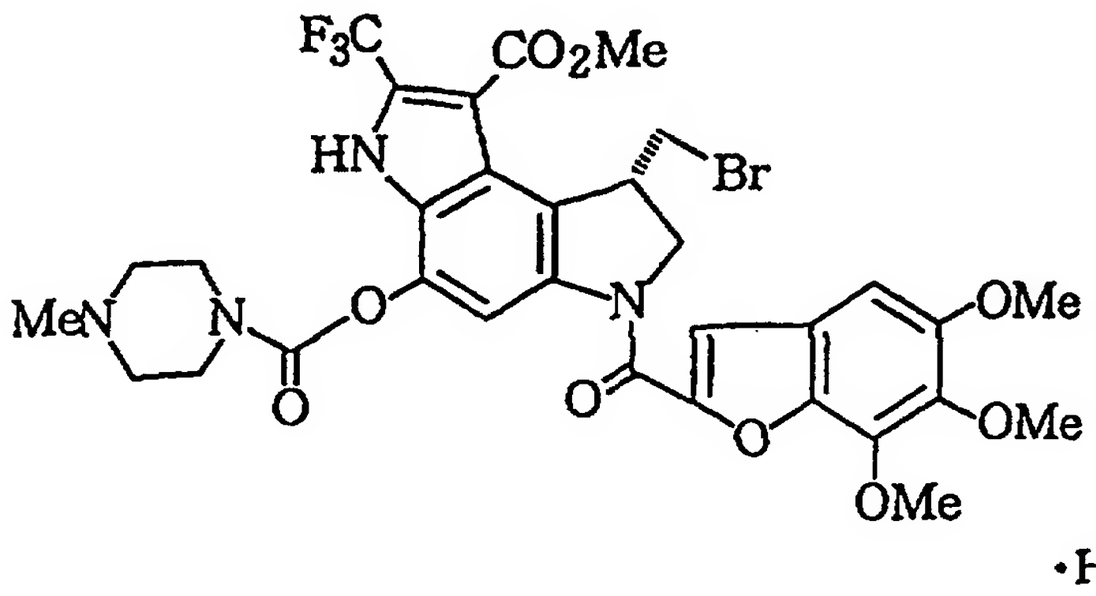
[0206] Methyl (1S)-1-bromomethyl-5-hydroxy-7-trifluoromethyl-3-(5,6,7-trimethoxybenzofuran-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 11.8 mg (22 μmol) of methyl (7bR,8aS)-6-trifluoromethyl-2-(5,6,7-trimethoxybenzofuran-2-ylcarbonyl)-1,2,8,8a-tetrahydrocyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one-7-carboxylate in the same manner as in Example 34 in a yield of 12.0 mg (89 %).

NMR ($CDCl_3$) δ : 3. 21(1H, t, J=11Hz), 3. 75(1H, dd, J=3. 0Hz, J=11Hz), 3. 90(3H, s), 3. 95(3H, s), 3. 99(3H, s), 4. 28(3H, s), 4. 49～4. 59(1H, m), 4. 67(1H, dd, J= 9Hz, J=11Hz), 4. 89(1H, d, J=12Hz), 6. 79(1H, s), 7. 69(1H, s), 8. 53(1H, s), 9. 87(1H, brs), 11.28(1H, brs)

$[\alpha]_D^{27}$= -48° (c=1.2, chloroform)

(EXAMPLE 92)

[0207]



[0208] Methyl (1S)-1-bromomethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-3-(5,6,7-trimethoxybenzofuran-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 12.0 mg (19 μmol) of methyl (1S)-1-bromomethyl-5-hydroxy-7-trifluoromethyl-3-(5,6,7-trimethoxybenzofuran-2-ylcarbonyl)-1,2,3,6-tetrahydropyrrolo[3,2-e]indol-8-carboxylate in the same manner as in Example 46 in a yield of 9.5 mg (66 %).

NMR ($CDCl_3$) δ : 2. 37(3H, s), 2. 52(4H, brs), 3. 27(1H, t, J=9Hz), 3. 64 (2H, brd, J=5Hz), 3. 78(3H, brd, J=6Hz), 3. 93 (3H, s), 3. 96(3H, s), 4. 00(3H, s), 4. 30 (3H, s), 4. 58～4. 67(2H, m), 4. 93(1H, d, J=9Hz), 6. 84(1H, s) ,7. 54(1H, s), 8. 36(1H, brs), 9. 74(1H, brs)

$[\alpha]_D^{25}$ = +30° (c=0.95, chloroform)

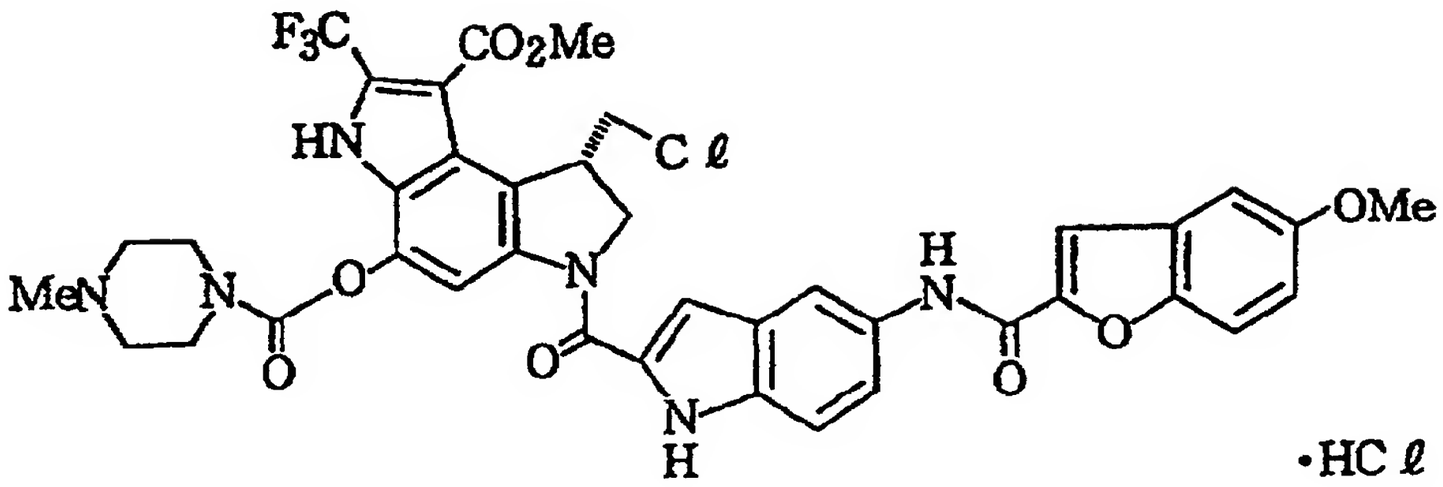
Hydrochloride salt: 9.4 mg (95 %)

NMR ($DMSOd_6$) δ:2.86(3H,brs),3.06～3.42(4H,m), 3.54(3H,t,J=9Hz),3.80(3H,s),3.81～3.88(1H,s),3.85(3H,s), 3.92(3H,s),4.18(3H,s),4.08～4.28(1H,m),4.35～4.55(2H,m), 4.66(1H, d, J=11Hz),4.75(1H, t, J=10Hz),7.07(1H,s),7.64 (1H,s), 8.21(1H, s),10.46(1H, brs),13.19(1H, brs)

$[\alpha]_D^{24}$ = +22° (c=0.13, methanol)

(EXAMPLE 93)

[0209]



[0210] Methyl (1S)-1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-3-[5-[5-methoxybenzofuran-2-ylcarbonyl) amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate hydrochloride was prepared by using 5.6 mg (8.2 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(5-methoxybenzofuran-2-yl-carbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 46 in a yield of 1.9 mg (27 %).

NMR ($CDCl_3$) δ:2.38(3H,s), 2.52(4H,brd,J=5Hz), 3.40(1H, t, J=10Hz), 3.66(2H,brd,J=5Hz), 3.76~3.95(3H,m), 3.87(3H,s), 3.99(3H,s), 4.55~4.65(2H,m), 4.75~4.85(1H,m), 7.07(1H,dd,J=3Hz, J=9Hz), 7.10(1H,brs), 7.13(1H,d, J=2Hz), 7.43~7.53(3H,m), 7.56(1H s), 8.36(1H,s), 8.38(1H,s), 9.37(1H,brs), 9.65(1H,brs)

$[\alpha]_D^{27}$ = +44° (c=0.16, chloroform)

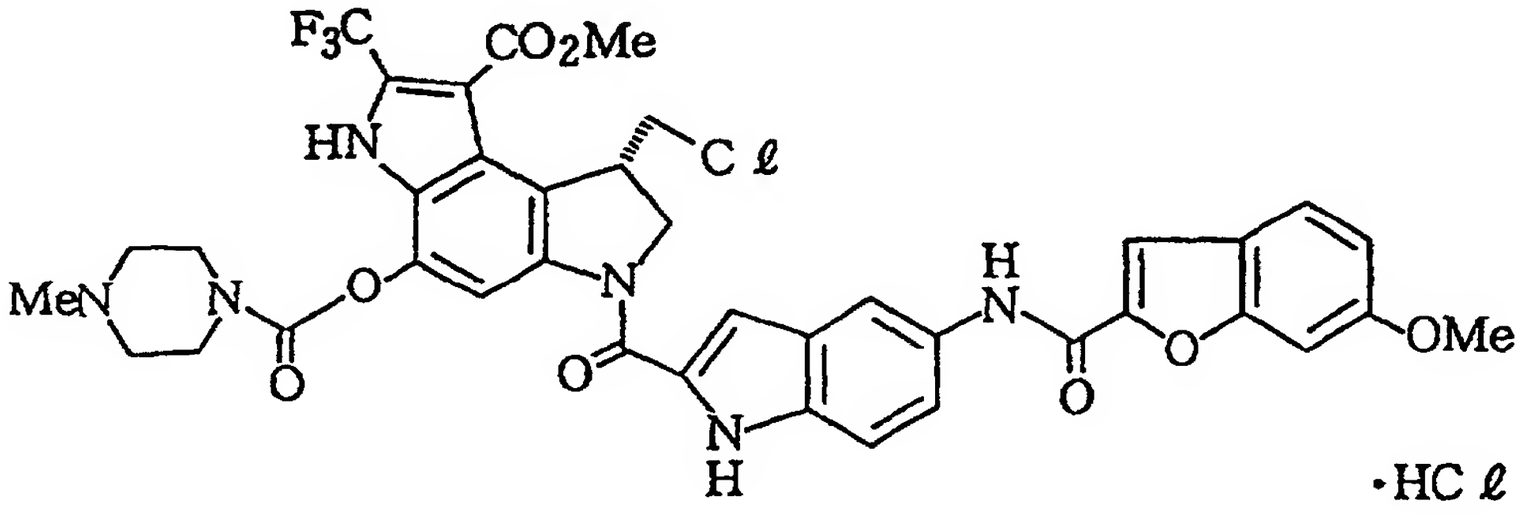
Hydrochloride salt:

NMR ($DMSOd_6$) δ : 2. 85(3H, brs), 3. 11~3.70(7H, m), 3. 80~3. 90(1H, m), 3. 83(3H, s), 3. 92(3H, s), 4.10~4. 23(1H, m), 4. 42(2H, brs), 4. 59(1H, d, J=11Hz), 4. 81(1H, t, J=11Hz), 7. 09(1H, dd. J=3Hz, J=9Hz), 7. 22(1H, s), 7.32 (1H, d, J=2Hz), 7. 50(1H, d, J=9Hz), 7. 63(2H, d, J=9Hz), 7. 70(1H, s), 8. 20(1H, s), 8. 22(1H, s), 10. 46(1H, s), 10. 85 (1H, brs), 11. 66(1H, s), 13. 17(1H, brs)

$[\alpha]_D^{24}$ = +12° (c=0.19, methanol)

(EXAMPLE 94)

[0211]



[0212] Methyl (1S)-1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-3-[5-(6-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 6.5 mg (10 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(6-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 46 in a yield of 3.6 mg (46 %).

NMR ($CDCl_3$) δ : 2. 51(3H, s), 2. 65(4H, brd, J=5Hz), 3. 40(1H, t, J=10Hz), 3. 65(2H, brd, J=5Hz), 3. 79(2H, brs), 3.84～3. 94(1H, m), 3. 90(3H, s), 3. 98(3H, s), 4. 51～4. 61(2H, m), 4. 72～4. 82(1H, m), 6. 96(1H, dd, J=2Hz, J=9Hz), 7. 06(2H, d, J=3Hz), 7. 42(2H, s), 7. 52～7. 60(2H, m), 8. 22(1H, s), 8. 33(1H, s), 3. 35(1H, s), 9. 43(1H, brs), 9. 90(1H, br)

$[\alpha]_D^{26}$ = +25° (c=0.36, chloroform)

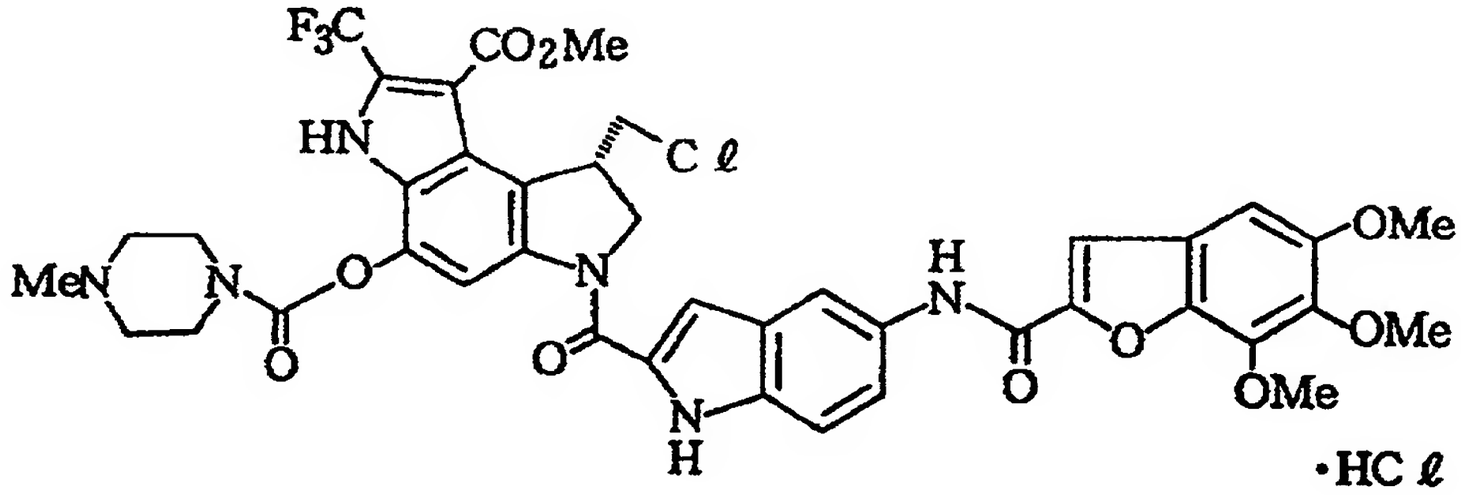
Hydrochloride salt: 3.7 mg (100 %)

NMR (DMSO d_6) δ : 2. 86(3H, brs), 3. 10～3. 70(7H, m), 3. 87(3H, s), 3. 88 ～3. 97(1H, m), 3. 92(3H, s), 4. 16 (1H, brs), 4. 42(1H, brs), 4. 60(1H, d, J=11Hz), 4. 81 (1H, t, J=10Hz), 7. 00(1H, dd, J=2Hz, J=9Hz), 7. 22(1H, s), 7. 27 (1H, s), 7. 50(1H, d, J= 9Hz), 7. 61(1H, d, J=9Hz), 7. 70(2H, d, J=8Hz), 8. 20(1H, s), 8. 21(1H, s), 10. 35(1H, s), 10. 55(1H, brs), 11. 64(1H, s), 13. 15(1H, brs)

$[\alpha]_D^{24}$ = +5.8° (c=0.13, methanol)

(EXAMPLE 95)

[0213]



[0214] Methyl (1S)-1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-3-[5-(5, 6, 7-trimethoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 5.7 mg (7.7 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-[5-(5,6,7-trimethoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 46 in a yield of 1.1 mg (16 %).

NMR ($CDCl_3$) δ : 2. 38(3H, s), 2. 53(4H, brd, J=5Hz), 3. 41(1H, dd, J=9Hz, J=11Hz), 3. 66(2H, brd, J=6Hz), 3. 83(2H, brd, J=5Hz), 3. 86～3. 94(1H, m), 3.93(3H, s), 3. 97(3H, s), 3. 99(3H, s), 4. 23(3H, s), 4. 55-4. 65(2H, m), 4. 80(1H, d, J=9Hz), 6. 86 (1H, s), 7. 10(1H, d, J=2Hz), 7. 46～7. 51(2H, m), 7. 54(1H, s), 8. 25(1H, s), 8. 36(1H, s), 8. 39(1H, s), 9. 38(1H, brs), 9. 70(1H, br)

$[\alpha]_D^{24}$ = +31° (c=0.11, chloroform)

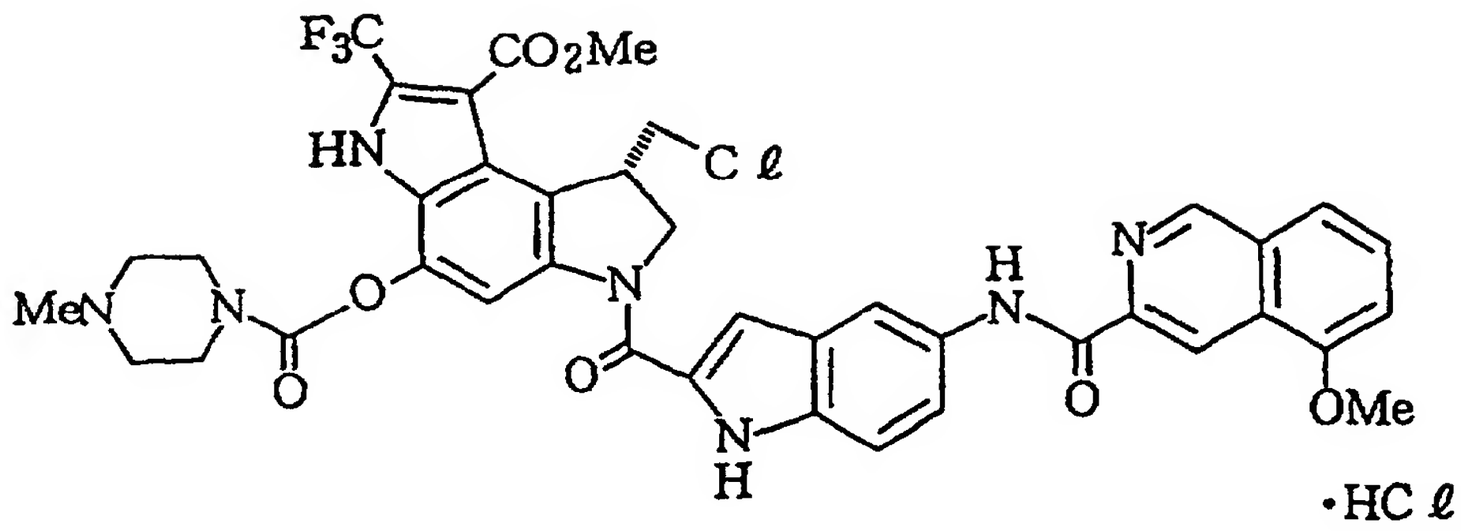
Hydrochloride salt: 1.0 mg (85 %)

NMR ($DMSOd_6$) δ : 2. 86(3H, s), 3. 10～3. 40(4H, m), 3. 51(2H, brs), 3. 60 ～3.70(1H, m), 3. 81(3H, s), 3. 86(3H, s), 3.89～3.98(1H, m), 3. 91(3H, s), 4.01～4.24 (1H, m), 4. 17(3H, s), 4. 42(2H, brs), 4. 60(1H, d, J=11Hz), 4. 81(1H, t, J=11Hz), 7. 08 (1H, s), 7. 22(1H, d, J=2Hz), 7.51(1H, d, J=9Hz), 7. 57(1H, dd, J=2Hz, J=9Hz), 7. 69(1H, s), 8. 18(1H, brs), 8. 20(1H, s), 10. 33(1H, s), 10. 70(1H, brs), 11. 67(1H, brs), 13. 16 (1H, brs)

$[\alpha]_D^{24}$ = +22° (c=0.13, methanol)

(EXAMPLE 96)

[0215]



[0216] Methyl (1S)-1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-3-[5-(5-methoxyisoquinolin-3-ylcarbonyl) amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 6.3 mg (9.1 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(5-methoxyisoquinolin-3-ylcarbonyl)amino-1H-indol-2-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 46 in a yield of 5.6 mg (75 %).

NMR ($CDCl_3$). δ : 2. 32(3H, s), 2. 49(4H, brs), 3.39(1H, t, J=10Hz), 3. 64 (2H, brs), 3. 73~3. 89(3H, m), 3. 98(3H, s), 4. 06(3H, s), 4. 50~4. 65(2H, m), 4. 77(1H, d, J=10Hz), 7. 03(1H, s), 7. 08(1H, dd, J=3Hz, J=6Hz), 7. 40(1H, d, J=9Hz), 7. 49(1H, d, J=9Hz), 7. 55~7. 66(2H, m), 8. 35(1H, s), 8. 38(1H, s), 9. 10(1H, s), 9.16(1H, s), 9.49 (1H, brs), 10. 25(1H, s)

$[\alpha]_D^{26}$ = +35° (c=0.56, chloroform)

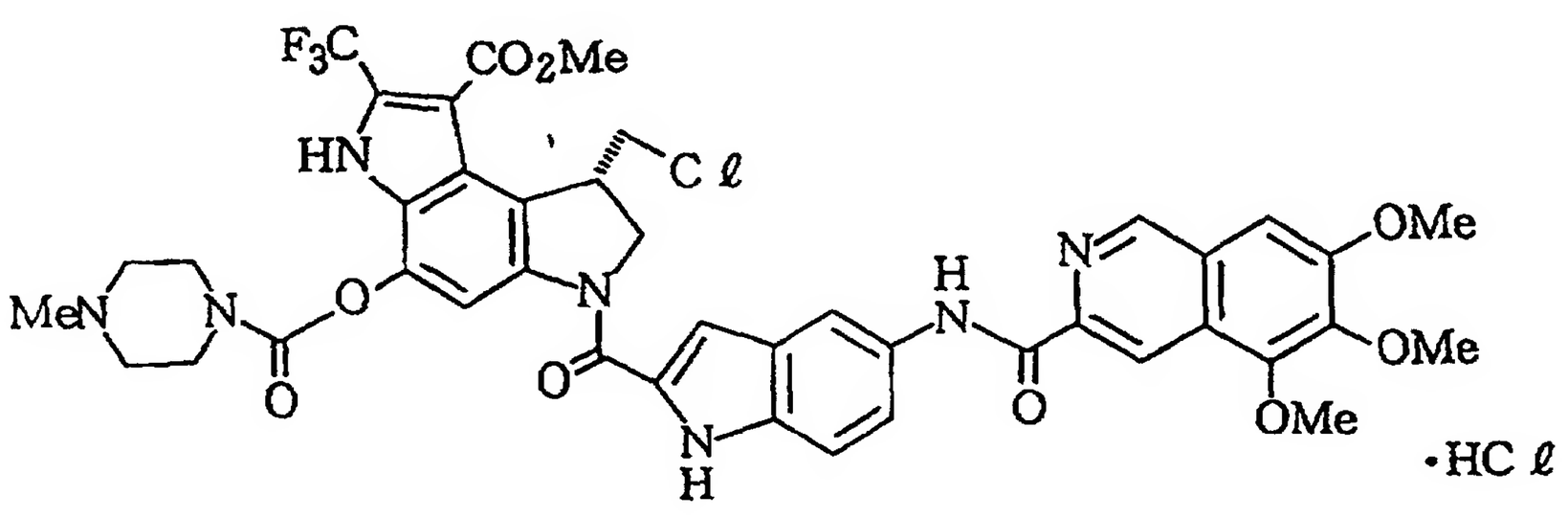
Hydrochloride salt: 5.6 mg (97 %)

NMR (DMSO d_6) δ : 2. 86(3H, d, J=5Hz), 3.12~3. 40(4H, m), 3. 52~3. 60 (2H, m), 3. 61~3. 70(1H, m), 3. 90~3. 98 (1H, m), 3. 92(3H, s), 4. 08(3H, s), 4, 18(1H, brd, J=13Hz), 4. 43(2H, brs), 4. 61(1H, d, J=11Hz), 4. 82(1H, t, J=10Hz), 7. 23(1H, brs), 7. 38(1H, d, J=8Hz), 7. 52(1H, d, J=9Hz), 7. 75(1H, brd, J=8Hz), 7. 78(1H, t, J=8Hz), 7. 85(1H, d, J=8Hz), 8. 21(1H, s), 8. 39(1H, brd), 8. 83(1H, brs), 9. 44(1H, brs), 10. 70(2H, brs), 11. 65(1H, brs), 13. 16(1H, brs)

$[\alpha]_D^{24}$ = +31° (c=0.13, methanol)

(EXAMPLE 97)

[0217]



[0218] Methyl(1S)-1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-3-[5-(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 20.4 mg (27 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-3-[5-(5,6,7-trimethoxyisoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 46 in a yield of 12.4 mg (52 %).

NMR ($CDCl_3$) δ: 2. 30(3H, s), 2. 47(4H, s), 3. 39(1H, t, J=9Hz), 3. 63(2H, s), 3. 78(2H, s), 3. 84(1H, dd, J=3Hz, J=11Hz),

3. 96(3H, s), 4. 04(3H, s), 4. 05(3H, s), 4. 12 (3H, s), 4. 52~4. 59(2H, m), 4. 74(1H, d, J=10Hz), 7. 01(1H, s), 7. 12(1H, s), 7. 38 (1H, d, J=9Hz), 7. 47(1H, d, J=9Hz), 8. 32(1H, s), 8. 38(1H, s), 8. 90(1H, s), 9. 02(1H, s), 9. 57(1H, br), 10. 20(1H, s)

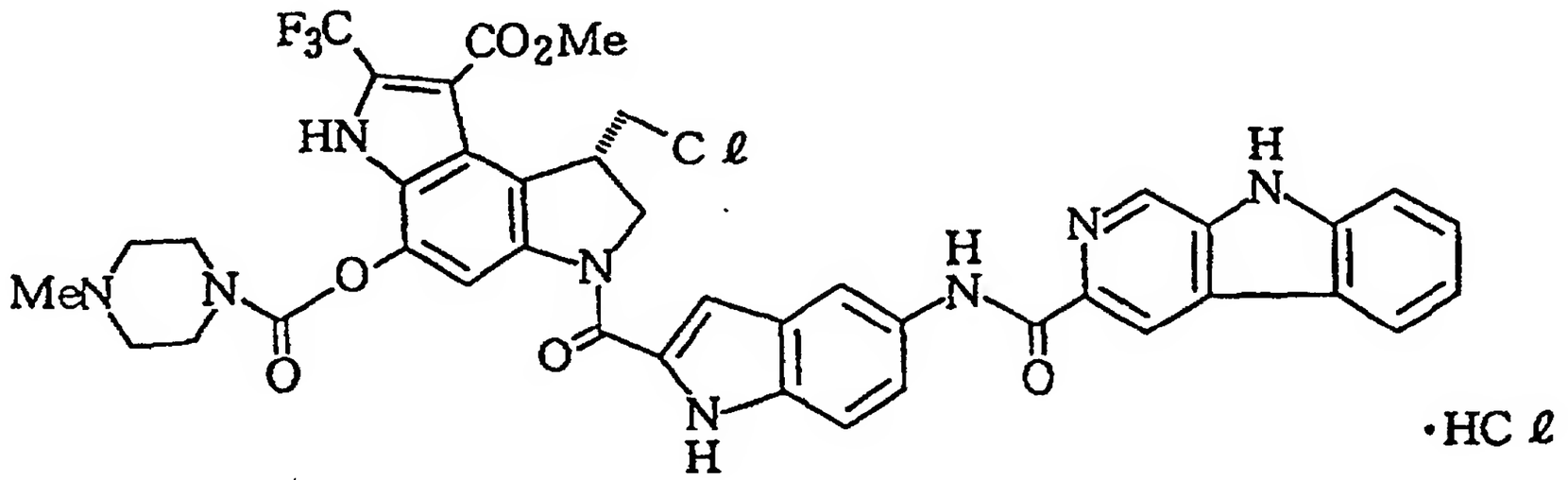
$[\alpha]_D^{26}$ = +28° (c=0.83, chloroform)

Hydrochloride salt:

$[\alpha]_D^{26}$ = +38° (c=0.40, methanol)

(EXAMPLE 98)

[0219]



[0220] Methyl (1S)-1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-3-[5-[(9H-pyrido[3,4-b]indol-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 20.3 mg (29 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-[(9H-pyrido[3,4-b]indol-3-ylcarbonyl)amino)-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 46 in a yield of 13.6 mg (57 %).

$[\alpha]_D^{26}$ = +51° (c=0.91, tetrahydrofuran)

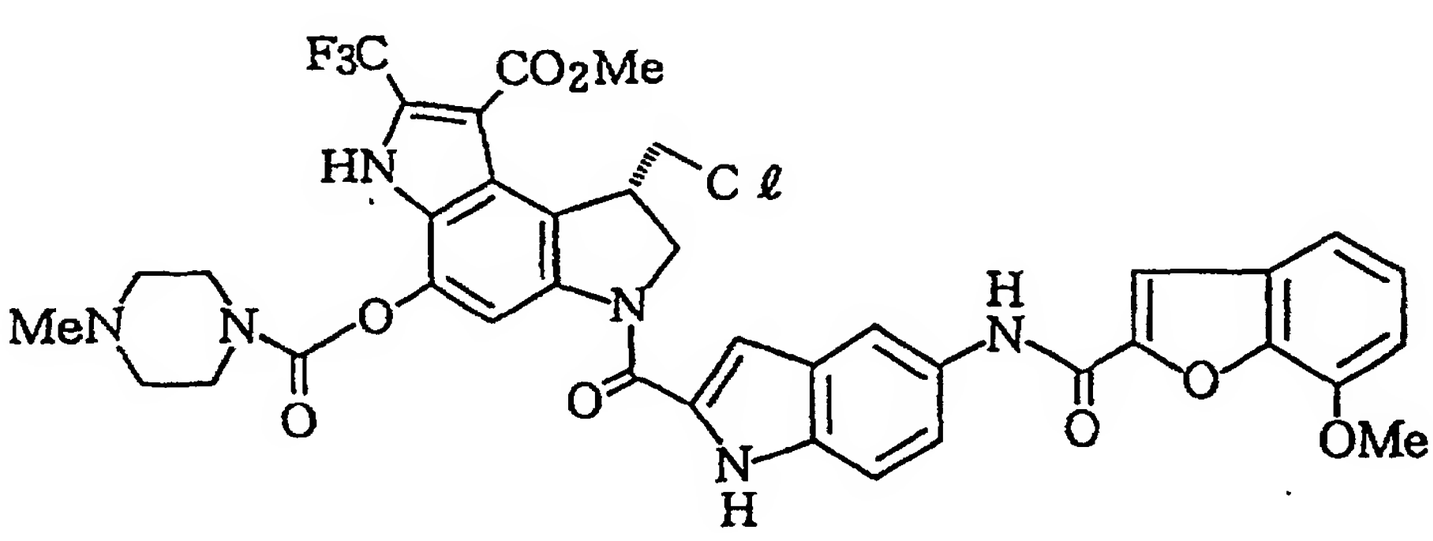
Hydrochloride salt:

NMR ($DMSOd_6$ δ : 2. 87(3H, brs), 3. 17~3. 43(3H, m), 3. 48~3. 63(4H, m), 3. 89~3. 95 (1H, m), 3. 92(3H, s), 4. 16 (1H, m), 4. 43(2H, brs), 4. 62(1H, d, J=11Hz), 4. 82(1H, t, J=10Hz), 7. 23(1H, s), 7. 37(1H, t, J=8Hz), 7. 54(1H, d, J=9Hz), 7. 66(1H, t, J=8Hz), 7. 73(1H, d, J=8Hz), 8. 21(1H, s), 8. 38(1H, s), 8. 46(1H, d, J=8Hz), 9. 06(1H, s), 9. 16 (1H, br), 10. 67 (1H, s), 10. 97(1H, br), 11. 65(1H, s), 12. 24(1H, s), 13. 16(1H, s)

$[\alpha]_D^{26}$ = +37° (c=0.40, dimethylformamide)

(EXAMPLE 99)

[0221]

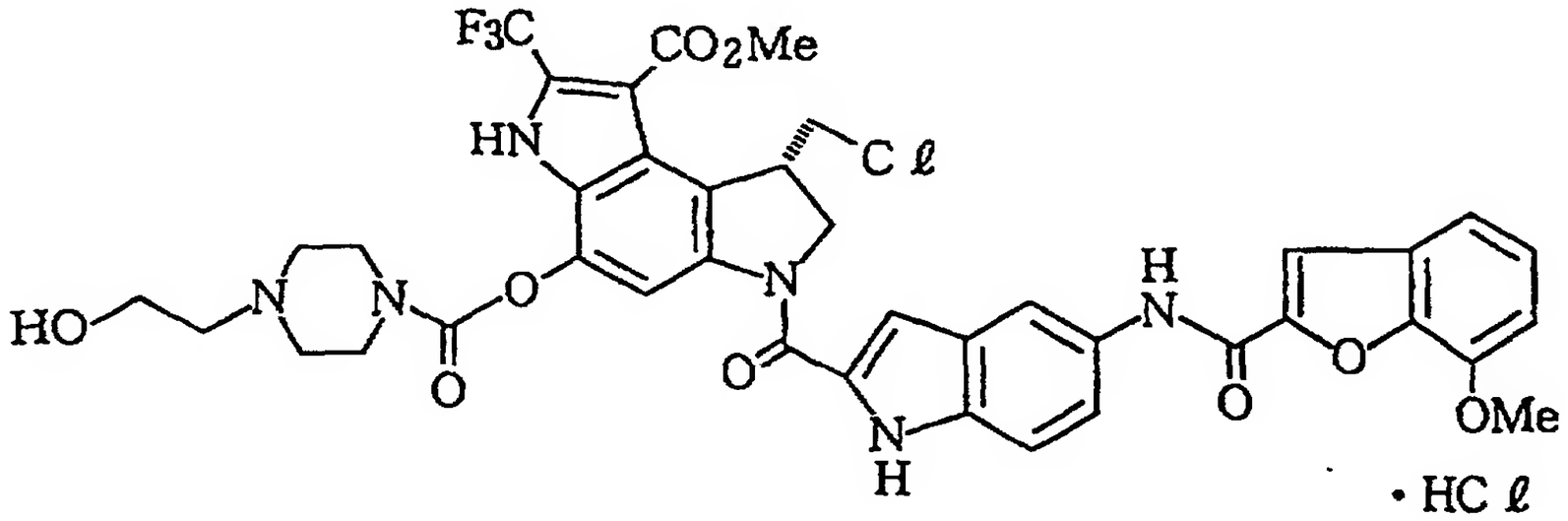


[0222] Methyl (1S)-1-chloromethyl-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 23.0 mg (34 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-[(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner

as in Example 46 in a yield of 17.4 mg (64 %).
NMR ($CDCl_3$) δ : 2. 30(3H, s), 2. 36~2. 48(4H, m), 2. 97(1H, t, J=10Hz), 3. 47(2H, m), 3. 67(1H, m), 3. 77(2H, s), 3. 94(3H, s), 4. 11(3H, s), 4. 23~4. 33(2H, m), 4. 51(1H, d, J=10Hz), 6. 90(1H, s), 6. 98(1H, d, J=7Hz), 7. 24~7. 34(3H, m), 7. 43(1H, dd, J=2Hz, J=9Hz), 7. 54 (1H, s), 7. 73(1H, s), 8. 44(1H, s), 8. 66(1H, s), 9. 56(1H, s), 10. 45 (1H, br)
$[\alpha]_D^{26}$ = +8.3° (c=1.2, chloroform)
Hydrochloride salt:
NMR ($DMSOd_6$) δ : 2. 86(3H, s), 3. 20~3. 69(6H, m), 3. 62(1H, t, J=10Hz), 3. 92(3H, s), 3. 94(1H, m), 4. 01(3H, s), 4. 19(1H, m), 4. 43(2H, m), 4. 63(1H, d, J=10Hz), 4. 78(1H, t, J=9Hz), 7. 07(1H, d, J=7Hz), 7.19(1H, d, J=2Hz), 7. 26 (1H, t, J=8Hz), 7. 34 (1H, d, J=7Hz), 7. 51(1H, d, J=9Hz), 7. 62(1H, dd, J=1Hz, J=9Hz), 7. 75(1H, s), 8. 20(1H, s), 8. 23(1H, d, J=1Hz), 10. 40(1H, s), 11. 21(1H, brs), 11. 63(1H, s), 13.11(1H, s)
$[\alpha]_D^{26}$ = +26° (c=0. 40, methanol)

(EXAMPLE 100)

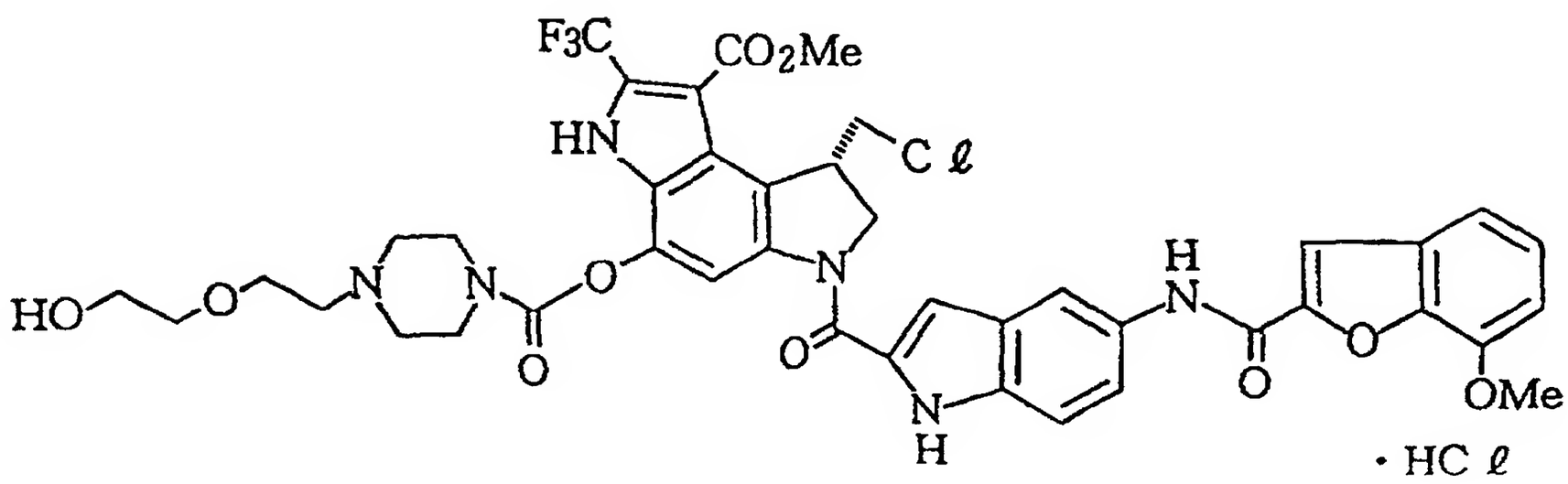
[0223]



[0224] Methyl (1S)-1-chloromethyl-5-[4-(2-hydroxyethyl)piperazin-1-ylcarbonyl)oxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate hydrochloride was prepared by using 25. 6 mg (37 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl)-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate and 6.8 μl (56 μmol) of 1-(2-hydroxyethyl)piperazine in the same manner as in Example 46 in a yield of 22.2 mg (69 %).
NMR ($CDCl_3$) δ : 2. 48~2. 74(6H, m), 3. 23(1H, t, J=9Hz), 3. 58(2H, brs), 3. 67 (2H, t, J=5Hz), 3. 76~3. 85(3H, m), 3. 97(3H, s), 4. 09(3H, s), 4. 46~4. 55(2H, m), 4. 67~4. 75(1H, m), 6. 97(1H, d, J=7Hz), 7. 04(1H, d, J=2Hz), 7. 26(1H, d, J=8Hz), 7.31 (1H, t, J=7Hz), 7. 43(1H, d, J=9Hz), 7. 50(1H, dd, J=2Hz, J=9Hz), 7. 60(1H, s), 8. 04(1H, s), 8. 40(1H, s), 8. 56(1H, s), 9. 52(1H, brs), 9. 99(1H, brs)
$[\alpha]_D^{25}$ = -15° (c=1.9, chloroform)
Hydrochloride salt:
NMR ($DMSOd_6$) δ : 3. 14~3. 55(6H, m), 3. 56~3. 77(3H, m), 3. 84(2H, brs), 3. 90~3. 97(1H, m), 3. 92(3H, s), 4. 00 (3H, s), 4. 10~4. 20(1H, m), 4. 43(2H, brs), 4. 60(1H, d, J=11Hz), 4. 81(1H, t, J=10Hz), 5. 43(1H, brs), 7. 10(1H, d, J=8Hz), 7. 23(1H, t, J=8Hz), 7. 37(1H, d, J=8Hz), 7. 51(1H, d, J=9Hz), 7. 62(1H, dd, J=2Hz, J=9Hz), 7.78 (1H, s), 8. 20(1H, s), 8. 21(1H, brs),10. 45(1H, s),10. 62(1H, brs), 11. 67(1H, brs), 13. 22(1H, brs)
$[\alpha]_D^{27}$ = +25° (c=0.75, methanol)

(EXAMPLE 101)

[0225]



[0226] Methyl(1S)-1-chloromethyl-5-[4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-ylcarbonyl]oxy-3-[5-(8-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 30.7 mg (44 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate and 11.6 mg (67 μmol) of 1-[2-(2-hydroxyethyl)ethyl]piperazine in the same manner as in Example 46 in a yield of 17.6 mg (45 %).

NMR ($CDCl_3$) δ :2. 55~2. 75(6H, m), 3. 31(1H, t, J=10Hz), 3.50~3.90 (10H, m), 3. 92~4. 02(1H, m), 3. 98(3H, s), 4. 08(3H, s), 4. 40~4. 59(2H, m), 4. 72(1H, d, J=10Hz), 6. 95(1H, d, J=8Hz), 7. 06(1H, s), 7. 20~7. 35(2H, m), 7. 40~7. 55(2H, m), 7. 61(1H, s), 8. 16(1H, s), 8. 35(1H, s), 8. 50(1H, s), 9. 43(1H, brs), 9. 95(1H, brs)

$[\alpha]_D^{27}$ = +19° (c=1.8, chloroform)

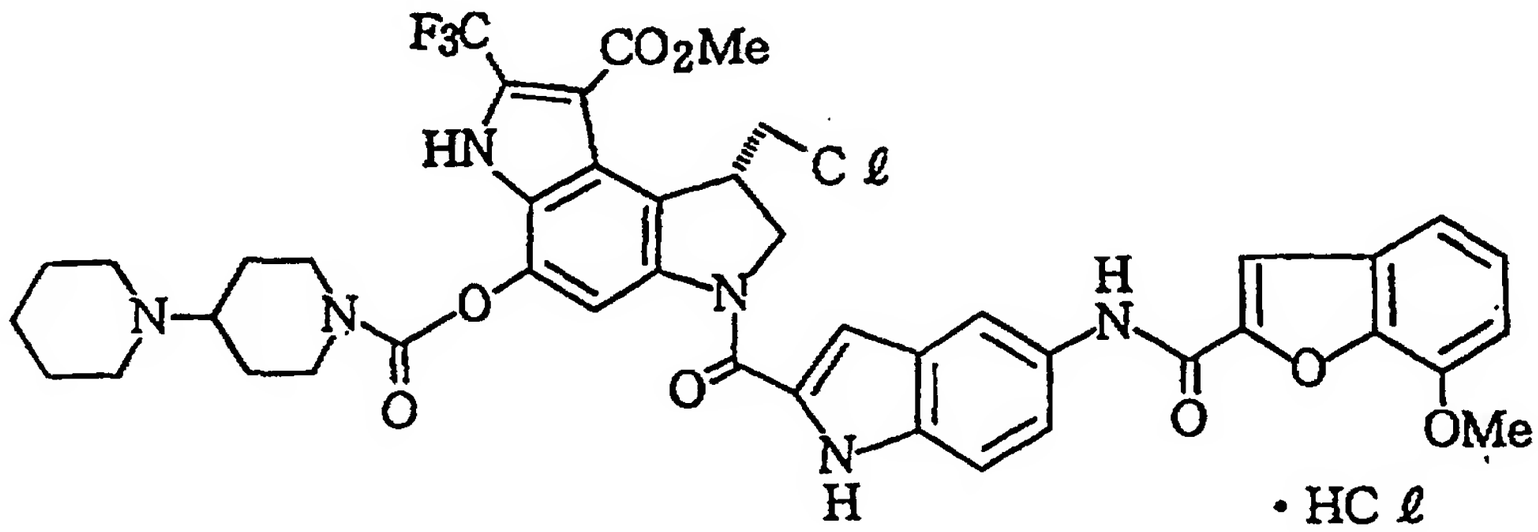
Hydrochloride salt: 13.8 mg (75 %)

NMR ($DMSOd_6$) δ : 3. 15~3. 45(6H, m), 3. 50~3. 78(7H, m), 3. 78~3. 90 (2H, m), 3. 90~3. 97(1H, m), 3. 92(3H, s), 4. 00(3H, s), 4. 17~4. 20(1H, m), 4. 42(2H, brs), 4. 59 (1H, d, J=11Hz), 4. 70~4. 85(1H, m), 4. 81(1H, t, J=10Hz), 7.11 (1H, d, J= 8Hz), 7. 23(1H, s), 7. 29(1H, t, J=8Hz), 7. 37(1H, d, J=8Hz), 7. 51(1H, d, J=9Hz), 7. 61 (1H, dd, J=2Hz, J=9Hz), 7. 78(1H, s), 8. 21(1H, brs), 10. 42(1H, s), 10. 45(1H, brs), 11. 67(1H, brs), 13. 22(1H, brs)

$[\alpha]_D^{27}$ = +19° (c=0.45, methanol)

(EXAMPLE 102)

[0227]



[0228] Methyl (1S)-1-chloromethyl-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-5-(4-piperidinopiperidin-1-ylcarbonyl)oxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate hydrochloride was prepared by using 24.1 mg (35 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoxomethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate and 0.6 mg (63 μmol) of 4-piperidinopiperidine in the same manner as in Example 46 in a yield of 16.5 mg (51 %).

NMR ($CDCl_3$) δ : 1. 35~1. 75(6H, m), 1. 80~1. 95(2H, m), 2. 52(6H, brs), 2. 70~2.85(1H, m), 2. 95~3. 25(3H, m), 3.

75(1H, t, J=10Hz), 3. 96(3H, s), 4. 09(3H, s), 4. 15～4. 30 (1H, m), 4. 32～4. 50(3H, m), 4. 55～4. 65(1H, m), 6. 95～7. 00(2H, m), 7. 25 (1H, d, J=8Hz), 7. 30(1H, t, J=8Hz), 7. 36～7. 50(2H, m), 7. 57(1H, s), 7.92(1H, brs), 8. 39 (1H, brs), 8. 61(1H, brs), 9. 63(1H, brs)

$[\alpha]_D^{24}$ = +5.0° (c=1.5, chloroform)

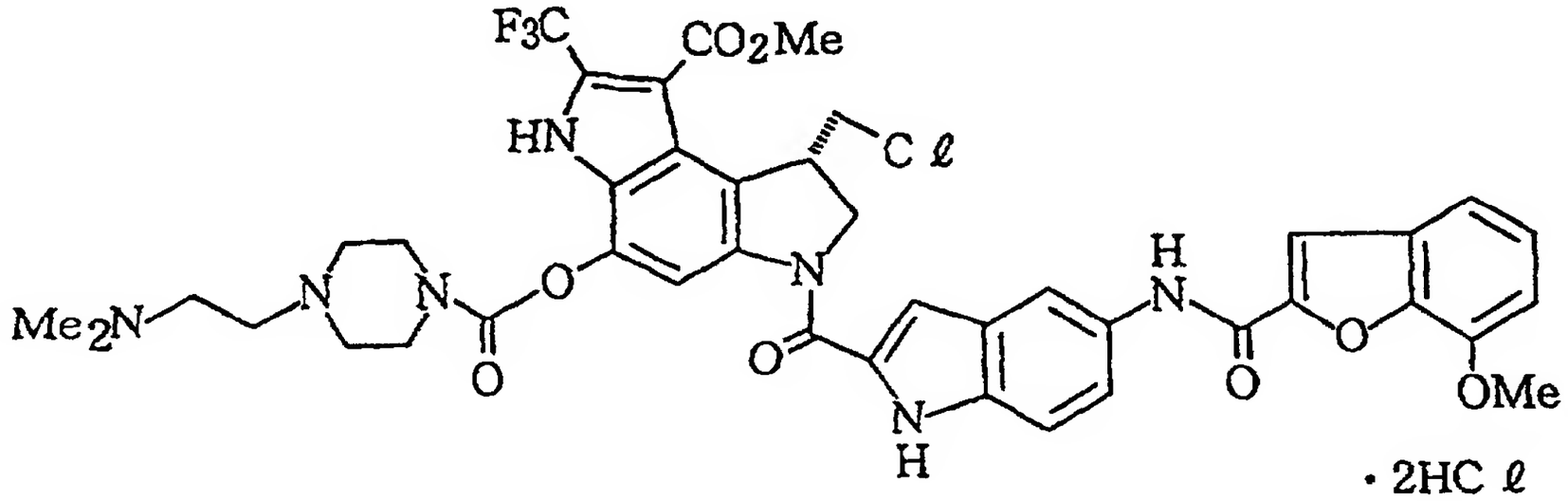
Hydrochloride salt:

NMR ($DMSOd_6$) δ : 1. 85(6H, brs), 2. 20(2H, brs), 2. 98(2H, brs), 3. 15 (1H, t, J=10Hz), 3. 30～3. 54(4H, m), 3. 64(1H, t, J=9Hz), 3. 88～3. 98(1H, m), 3. 91(3H, s), 4. 00 (3H, s), 4. 14～4. 26 (1H, m), 4. 88～4. 98 (2H, m), 4. 60(1H, d, J=11Hz), 4. 80(1H, t, J=10Hz), 7. 10 (1H, d, J=8Hz), 7. 22 (1H, brs), 7. 28(1H, t, J=8Hz), 7. 37(1H, d, J=7Hz), 7. 51 (1H, d, J=9Hz), 7. 61(1H, dd, J=2Hz, J=9Hz), 7. 78(1H, s), 8. 15(1H, s), 8. 32(1H, s), 10.16(1H, brs), 10. 40(1H, s), 11. 68(1H, s), 13. 20(1H, s)

$[\alpha]_D^{27}$ = +2.2° (c=0.47, methanol)

(EXAMPLE 103)

[0229]



[0230] Methyl (1S)-1-chloromethyl-5-[4-(2-dimethylaminoethyl)piperazin-1-ylcarbonyl)oxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate hydrochloride was prepared by using 25.2 mg (37 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate and 8.6 mg (55 μmol) of 4-(2-dimethylaminoethyl)piperazine in the same manner as in Example 46 in a yield of 9.9 mg (28 %).

NMR ($CDCl_3$)

NMR ($CDCl_3$) δ : 2. 19(3H, s) , 2. 20(3H, s), 2. 30～2. 60(8H, m), 3. 00～3. 16(1H, m), 3. 40～3. 58(2H, m), 3. 58～3. 75(3H, m), 3. 89(3H, s), 4. 03(3H, s), 4. 35(2H, brs), 4. 56(1H, d, J=8Hz), 6. 86～6. 94(2H, m), 7. 16～7. 26(2H, m), 7. 29～7. 36(1H, m), 7. 38～7. 44(1H, m), 7. 50(1H, s), 7. 86(1H, brs), 8. 34(1H, s), 8. 55(1H, s), 9. 26(1H, brs), 9. 50(1H, brs)

$[\alpha]_D^{24}$ = +7.2° (c=0.82, chloroform)

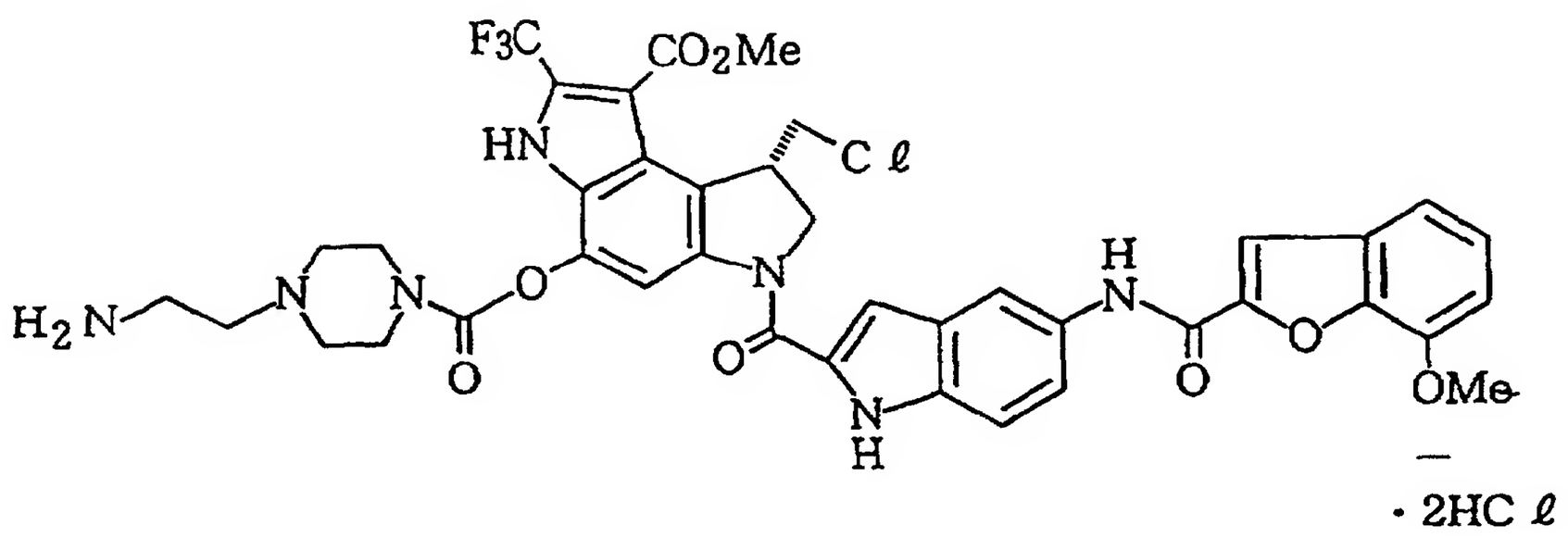
Hydrochloride salt:

NMR ($DMSOd_6$) δ : 2. 80～2. 92(8H, m), 3. 20～3. 58 (8H, m), 3. 65(1H, dd, J=7Hz, J=11Hz), 3. 90～3. 98(1H, m), 3. 92(3H, s), 4. 00(3H, s), 4. 08～4. 24(1H, m), 4. 40～4. 47 (2H, m), 4. 60(1H, d, J=11Hz), 4. 81(1H, dd, J=9Hz, J=11Hz), 7.10(1H, d, J= 8Hz), 7. 22(1H, d, J=2Hz), 7. 32(1H, t, J=8Hz), 7. 37(1H, d, J=8Hz), 7. 51(1H, d, J=9Hz), 7. 62(1H, dd, J=2Hz, J=9Hz), 7. 78(1H, s), 8.19(1H, s), 8. 22(1H, s), 10. 45(1H, s), 11. 67(1H, s), 13. 20(1H, s)

$[\alpha]_D^{27}$ = +2.3° (c=0.27, methanol)

(EXAMPLE 104)

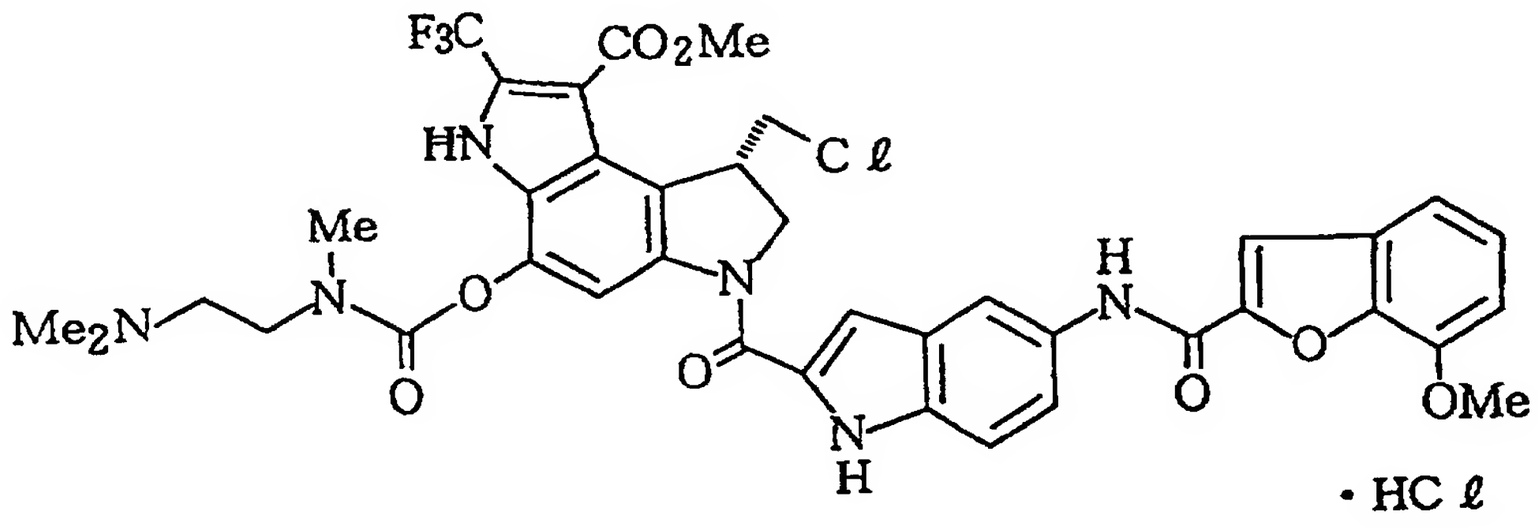
[0231]



[0232] Methyl (1S)-5-[4-(2-aminoethyl)piperazin-1-ylcarbonyl)oxy-1-chloromethyl-3-[5-(8-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate hydrochloride was prepared by using 26.0 mg (38 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-[5-(8-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate and 7.4 μl (56 μmol) of 4-(2-aminoethyl)piperazine in the same manner as in Example 46 in a yield of 9.1 mg (27 %).
NMR ($CDCl_3$) δ : 2. 40~2. 65(6H, m), 2. 80~2. 90(2H, m), 3. 30~3. 42(1H, m), 3. 55~3. 95(5H, m), 3. 99(3H, s), 4. 08(3H, s), 4. 50~4. 62(2H, m), 4. 75~4. 85(1H, m), 6. 96(1H, d, J=7Hz), 7. 10(1H, s), 7. 26~7. 33(2H, m), 7. 47(1H, d, J=9Hz), 7. 50~7. 55(1H, m), 7. 61(1H, s), 8. 19(1H, s), 8.37(1H, s), 8. 53(1H, s), 9. 10(1H, brs), 9. 45(1H, brs)
$[\alpha]_D^{23}$ = +25° (c=0.39, tetrahydrofuran)
Hydrochloride salt:
NMR R ($DMSOd_6$) δ: 2. 80~3. 70(10H, m), 3. 64(1H, t, J=8Hz), 3. 87~3. 98 (1H, m), 3. 92(3H, s), 4. 00(3H, s), 4. 10~4. 24(1H, m), 4. 43(2H, brs), 4. 60(1H, d, J= 12Hz), 4. 82(1H, t, J=10Hz), 7. 11(1H, d, J=8Hz), 7. 23(1H, s), 7. 39 (1H, t, J=8Hz), 7. 47 (1H, d, J=8Hz), 7. 61(1H, d, J=9Hz), 7. 71(1H, brd, J=9Hz), 7. 88(1H, s), 8. 31(1H, s), 8. 41(1H, s), 10. 58(1H, s), 11. 78(1H, brs), 13. 34(1H, brs)
$[\alpha]_D^{27}$ = +11° (c=0.21, methanol)

(EXAMPLE 105)

[0233]



[0234] Methyl (1S)-1-chloromethyl-3-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-5-(N,N,N'-trimethylethylenediamine-1-ylcarbonyl)oxy-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 23.9 mg (35 μmol) of methyl (1S)-1-chloromethyl-5-hydroxy-3-(7-methoxybenzofuran-2-ylcarbonyl)amino-1H-indol-2-ylcarbonyl]-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate and 6.6 μl (52 μmol) of N,N,N'-trimethylethylenediamine in the same manner as in Example 46 in a yield of 11.9 mg (42 %).
NMR ($CDCl_3$) δ : 2. 34(6H, s), 2. 45~2. 58(2H, m), 2. 73~2. 58(2H, m), 3. 07(3H, s), 3. 35(1H, t, J=10Hz), 3. 84(1H, d, J=11Hz), 3. 96(3H, s), 4. 06(3H, s), 4. 30~ 4. 50(2H, m), 4. 72(1H, t, J=10Hz), 6. 92(1H, d, J=8Hz), 7. 07(1H, s), 7.

23(1H, d, J=8Hz), 7. 28 (1H, t, J=8Hz), 7. 31～7. 45(2H, m), 7. 61(1H, s), 8. 26(1H, brs), 8. 38(1H, brs), 8. 47(1H, brs), 9. 63(1H, brs), 10. 40(1H, brs)

$[\alpha]_D^{27}$ = +99° (C=0.60, chloroform)

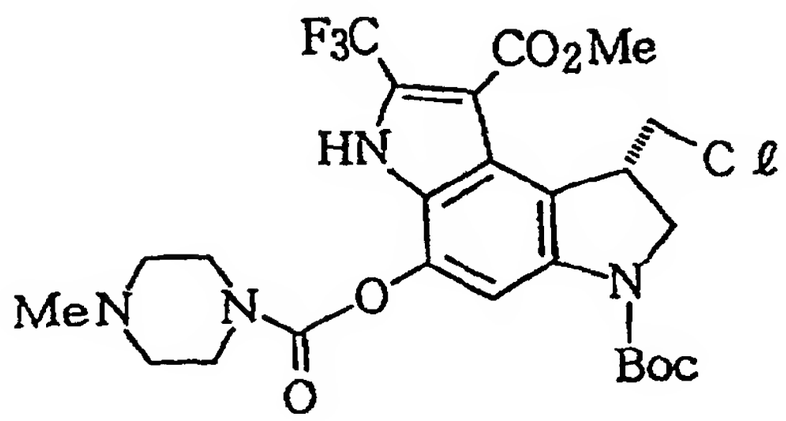
Hydrochloride salt: 8.4 mg (67 %)

$[\alpha]_D^{27}$ = +35° (c=0.11, methanol)

SIMS (positive, glycerol) m/z: 809 $[M+H]^+$

(EXAMPLE 106)

[0235]



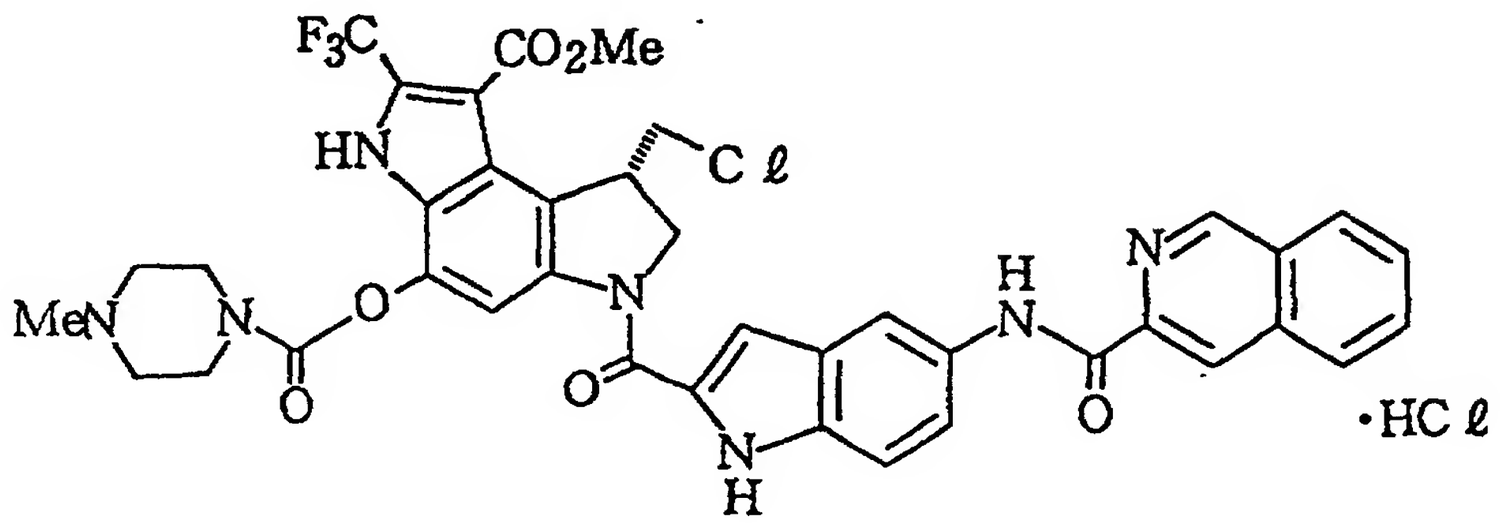
[0236] Methyl (1S)-3-(t-butoxycarbonyl)-1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 48.9 mg (0.1 mmol) of methyl (1S)-3-(t-butoxycarbonyl)-1-chloromethyl-5-hydroxy-7-trifluoromethyl-l,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate in the same manner as in Example 46 in a yield of 52.3 mg (91 %).

NMR ($CDCl_3$) δ : 1. 57(9H, s), 2. 37(3H, s), 2. 50(4H, brs), 3. 38(1H, t, J =10Hz), 3. 62(2H, brs), 3. 75(2H, brs), 3. 80 (1H, dd, J=3Hz, J=11Hz), 3. 96(3H, s), 4. 00 (1H, dd, J=9Hz, J=11Hz), 4. 21(1H, d, J=11Hz), 4. 35(1H, m), 7. 98(1H. brs), 9. 59(1H, br)

$[\alpha]_D^{25}$ = -51° (c=0.20, chloroform)

(EXAMPLE 107)

[0237]



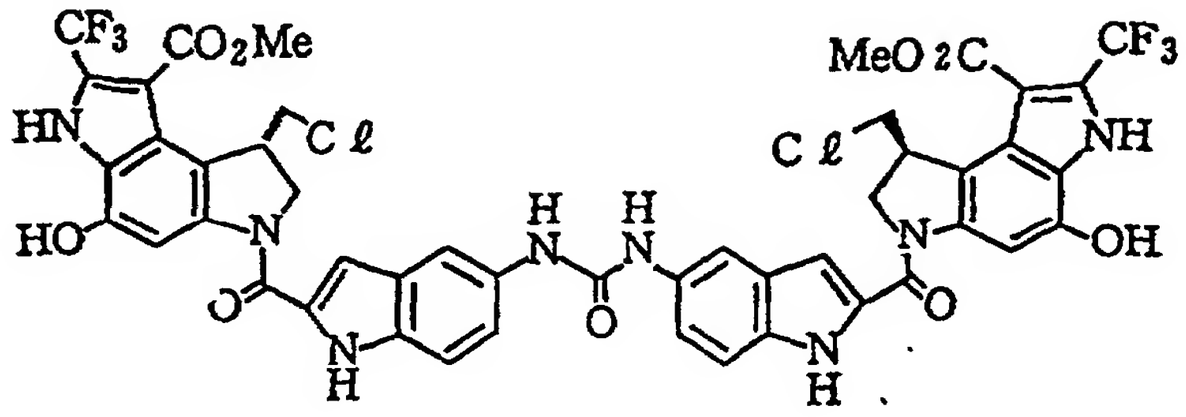
[0238] Methyl (1S)-1-chloromethyl-3-[5-[(isoquinolin-3-ylcarbonyl)amino]-1H-indol-2-ylcarbonyl]-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate was prepared by using 40.2 mg (70 μmol) of methyl (1S)-3-(t-butoxycarbonyl)-1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate and 23.2 mg (70 μmol) of 3-(5-isoquinolin-3-ylcarbonyl)amino-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 40.5 mg (74 %). Hydrochloride salt:

NMR ($DMSOd_6$) δ : 2. 88(3H, s), 3. 20～3. 38(4H, m), 3. 52(2H, m), 3. 65 (1H, brs), 3. 92(3H, s), 3. 95(1H, m), 4. 19 (1H, d, J=12Hz), 4. 43(2H, brs), 4. 61(1H, d, J=11Hz), 4. 82(1H, t, J=10Hz), 7. 23(1H, s), 7. 52(1H, d, J=9Hz), 7. 76 (1H, d, J=9Hz), 7. 86(1H, dd, J=1Hz, J=7Hz), 7. 92(1H, dt, J=1Hz, J=7Hz), 8. 21(1H, s), 8. 27(1H, d, J=8Hz), 8. 32 (1H, d, J=8Hz), 8. 41(1H, s), 8. 73(1H, s), 9. 49(1H, s), 10. 45(1H, br), 10. 71(1H, s), 11. 65(1H, s), 13. 14(1H, s)

$[\alpha]_D^{25}$ = +40° (c=0.20, dimethylformamide)

(EXAMPLE 108)

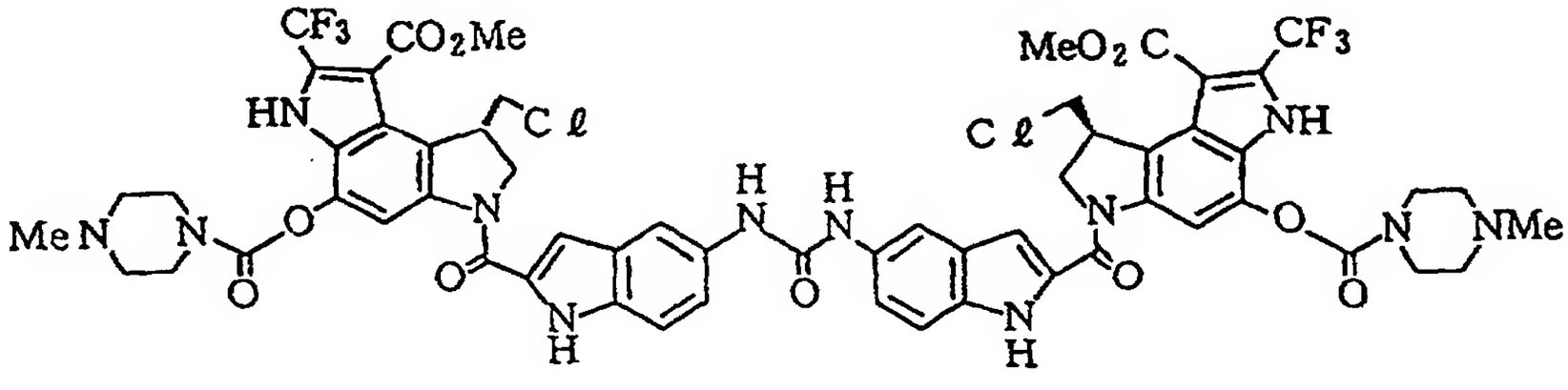
[0239]



[0240] (S,S)-3-3'-[Carbonylbis(imino-1H-indol-5,2-dicarbonyl)]bis-[1-chloromethyl-5-hydroxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylic acid methyl ester] was prepared by using 4.4 mg (12 μmol) of 5,5'-(carbonyldiimino)bis-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 10.2 mg (86 %).
NMR ($DMSOd_6$) δ: 3. 51(1H×2, t, J=11Hz), 3. 81(1H×2, m), 3 .88(3H× 2, s), 4. 28 (1H × 2, m), 4. 53(1H × 2, d, J=11Hz), 4. 70(1H×2, t, J=11Hz), 7. 09 (1H × 2, s), 7. 28(1H×2, dd, J=2Hz, J=9Hz), 7. 42(1H×2, d, J=9Hz), 7. 86 (1H×2, s), 7. 95(1H× 2, brs), 8. 47(1H×2, s), 10. 57(1H×2, s), 11.59(1H×2, s), 13. 08(1H×2, brs)
$[\alpha]_D^{23}$ = +74° (c=0.16, tetrahydrofuran)

(EXAMPLE 109)

[0241]



[0242] (S,S)-3-3'-[Carbonylbis(imino-1H-indol-5,2-dicarbonyl)]bis-[1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylic acid methyl ester] was prepared by using 11.5 mg (20 μmol) of methyl(1S)-3-(t-butoxycarbonyl)-1-chloromethyl-5-(4-methylpiperazin-1-ylcarbonyl)oxy-7-trifluoromethyl-1,2,3,6-tetrahydropyrrolo[3,2-e]indole-8-carboxylate and 3.8 mg (10 μmol) of 5,5'-(carbonyldiimino)bis-1H-indole-2-carboxylic acid in the same manner as in Example 6 in a yield of 8.4 mg (65 %).
NMR ($DMSOd_6$) δ: 2. 29(3H×2, s), 2. 50(4H×2, br), 3. 49(2H×2, brs), 3. 61(1H×2, t, J=9Hz), 3. 72(2H×2, brs), 3. 90 (3H×2, s), 3. 93(1H×2, dd, J=3Hz, J= 11Hz), 4. 42(1H×2, m), 4. 59(1H×2, d, J=11Hz), 4. 77(1H×2, t, J=10Hz), 7. 11 (1H×2, s), 7. 28(1H×2, d, J=9Hz), 7. 43(1H×2, d, J=9Hz), 7. 88(1H×2, s), 8. 10(1H×2, br), 8.50 (1H×2, s), 11. 55 (1H×2, s), 13. 10(1H×2, br)
$[\alpha]_D^{25}$ = +36° (c=0.62, chloroform:methanol = 5:1) Hydrochloride salt:
$[\alpha]_D^{25}$ = +34° (c=0.20, dimethylformamide)

EFFECTS OF INVENTION

Experiment 1

Activity against Tumor Cell Growth

[0243] Using a culture medium RPMI1640 supplemented with 10% inactivated bovine fetal serum, 2mM glutamine, 100μg/ml kanamycin sulfate, and 5 μM 2-hydroxyethyldisulfide (This culture medium is hereinafter referred to simply as "culture medium"), P388 mouse leukemia cells were diluted to a conentration of 1.5×10^5 cells/ml in the culture medium, and were placed in each well of 96-well multiplate in 60 μl portions. Separately, the test compound was dissolved in dimethylsulfoxide and was adequately diluted with the culture medium. The diluted solution containing test compound was added to the wells of the above plate respectively in 60 μl portions. Then the cells were incubated in a CO_2-incubator (5% CO_2, 37° C) for 72 hours.

[0244] The surviving cell numbers were measured according to the Mosmann's method (J. Immunol. Meth., 65 55-63, 1983) as follows. A 2.5 mg/ml solution of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) in Dulbecco's phosphate buffer solution (PBS) was prepared and added to each of the wells by 20 μl. The cells were further incubated for 3 hours. A 150 μl portion of 0.04N hydrochloric acid-isopropanol solution was added to each of the wells, and MTT-formazane formed was allowed to dissolve by pipetting. The absorbance of the solutions was measured at 540 nm taking the no-cell-containing solution as the background. The 50% growth inhibition concentration (IC_{50}) was produced from ratio of the absorbances of the treated samples to the absorbance of the no-medicine-treated sample, and from the concentration of the test compound.

[0245] The results are shown in Table 1.

Table 1 :

Inhibitory Activity against Tumor Cell Growth					
Example No.	IC_{50} (ng/ml)	Example No.	IC_{50} (ng/ml)	Example No.	IC_{50} (ng/ml)
6	0.24	31	0.10	66	0.77
8	0.21	32	0.09	67	0.026
9	0.76	33	0.17	68	0.051
10	0.52	34	0.15	69	0.046
11	0.67	36	1.3	70	2.0
13	0.21	37	0.61	74	1.3
14	0.10	39	0.20	75	0.74
15	0.83	40	0.08	76	0.20
16	0.16	41	1.6	77	0.23
17	0.09	42	0.13	78	0.33
18	0.09	43	0.10	79	2.1
19	0.11	44	0.07	84	1.7
20	0.24	45	0.12	86	1.1
22	0.23	46	22	90	0.90
23	0.86	47	31	97	5.8
24	0.53	48	80	98	5.7
25	0.63	49	89	107	4.6
27	0.17	50	4.5	108	0.0070
28	0.11	63	0.55	109	53
29	1.2	64	3.9		
30	0.22	65	0.11		

Experiment 2

Antineoplastic Activity

[0246] The test compound was dissolved in dimethylsulfoxide, and the solution was adequately diluted with 10%

Emulfore EL620 (produced by Rhone Poulenc Co.) to prepare the test compound solution. The antineoplastic activity was evaluated as below.

(1) Evaluation with mice having P388 cells transplanted in abdominal cavity:

[0247] To the abdominal cavity of a female mouse (CDF_1 strain, 8 to 9 week age), 1×10^6 P388 cells were transplanted. Next day, the test medicine solution was injected intraperitonealy in a single dose. Five to eight mice were employed for the solvent-dosed control group, and two mice were employed for each of the dosed groups. The antineoplastic effect was evaluated by the ratio (T/C, %) of the average survival days of the dosed group (T) to the average survival days of the solvent-dosed control group(C). The T/C ratio of 130 % or more is evaluated to be effective. The results are shown in Table 2.

Table 2 :

Antineoplastic Activity for Mice Having P388 Cells Transplanted in Abdominal Cavity					
Example No.	i.p. Dosage (mg/kg)	T/C (%)	Example No.	i.p. Dosage (mg/kg)	T/C (%)
6	0.5	206	34	0.125	189
8	1.0	198	36	0.125	384
20	0.125	194	46	4	221
22	0.125	169	47	0.5	Both cured
23	0.25	Both cured	48	0.5	Both cured
24	0.125	Both cured	49	0.5	Both cured
"Cured" : Survived for 60 days or longer					

(2) Evaluation with mice having Sarcoma-180 cells transplanted subcutaneously:

[0248] To the lateral region of a female mouse (CDR strain, 5 to 6 week age), 3.6×10^6 to 5×10^6 Sarcoma-180 cells were transplanted subcutaneously. Next day, the test medicine solution was injected into the tail vein in a single dose. Eight to twelve mice were employed for the solvent-dosed control group, and five mice were employed for the dosed group. Six days after the dosage, the tumor was cut out, and the weight thereof was measured. The antineoplastic effect was evaluated by the ratio (T/C) of the average tumor weight of the dosed group (T) to the average tumor weight of the solvent-dosed control group(C). The results are shown in Table 3.

Table 3 :

Antineoplastic Activity for Mice Having Sarcoma-180 Cells Transplanted subcutaneously					
Example No.	i.v. Dosage (mg/kg)	T/C	Example No.	i.v. Dosage (mg/kg)	T/C
10	0.5	0.15	31	0.125	0.24
11	1.0	0.06	32	0.125	0.23
12	1.0	0.11	34	0.25	0.37
13	0.25	0.11	36	0.25	0.14
14	0.5	0.07	37	0.25	0.24
15	0.5	0.11	43	0.125	0.25
16	0.5	0.17	47	1.0	0.19
17	0.25	0.25	48	1.0	0.08
18	0.25	0.25	49	0.5	0.12
19	0.25	0.22	50	4.0	0.15
20	0.25	0.36 *	51	4.0	0.25
23	0.25	0.16	52	1.0	0.12
24	0.25	0.17	53	4.0	0.20
27	0.125	0.19	54	0.25	0.15
28	0.25	0.28			

* (n = 4)

(3) Evaluation with mice having Colon-26 cells transplanted subcutaneously:

[0249] To the lateral region of a female mouse (CDF_1 strain, 8 to 12 week age), 1×10^6 Colon-26 cells were transplanted subcutaneously. On the sixth day after the transplantation, the test medicine solution was injected into the tail vein in a single dose. Seven to twelve mice were employed for the solvent-dosed control group, and five mice were employed for the dosed group. One week after the dosage, the tumor was cut out, and the weight thereof was measured. The antineoplastic effect was evaluated by the ratio (T/C) of the average tumor weight of the dosed group (T) to the average tumor weight of the solvent-dosed control group (C).
The results are shown in Table 4.

Table 4 :

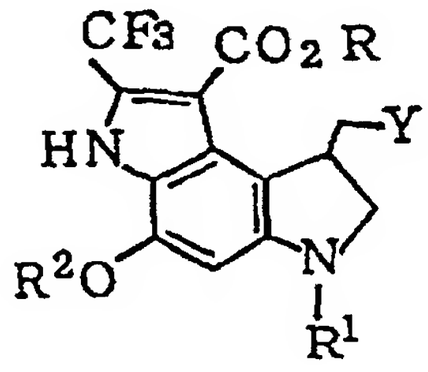
Antineoplastic Activity for Mice Having Colon-26 Cells Transplanted subcutaneously					
Example No.	i.v. Dosage (mg/kg)	T/C	Example No.	i.v. Dosage (mg/kg)	T/C
10	0.5	0.15	75	0.5	0.17
12	1.0	0.16	76	0.5	0.06
13	0.25	0.17	77	0.5	0.06
14	0.5	0.05	78	0.125	0.26
16	0.5	0.16	79	0.5	0.09
17	0.25	0.18	86	0.5	0.4
18	0.25	0.07	90	1.0	0.31
20	0.25	0.15	97	0.5	0.11
23	0.25	0.12	98	0.5	0.29
24	0.25	0.11	99	2.0	0.05
47	1.0	0.07	107	0.5	0.07
48	1.0	0.06	108	0.0156	0.06
49	0.5	0.09	109	0.25	0.07
63	0.5	0.04			

INDUSTRIAL USEFULNESS

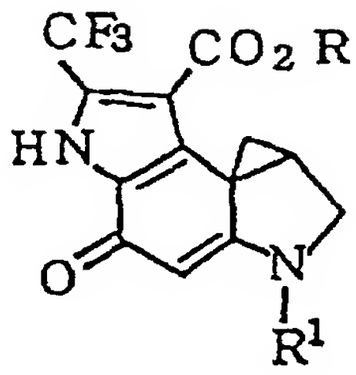
[0250] As shown clearly from the above experiments, the compounds of the present invention have antineoplastic activity, and high selectivity to cancer cells, and therefor are useful.

Claims

1. Trifluoromethylpyrroloindolecarboxylic acid ester derivatives represented by the general formula (1) and (2) below, optical isomers thereof, and pharmaceutically acceptable salts thereof: .



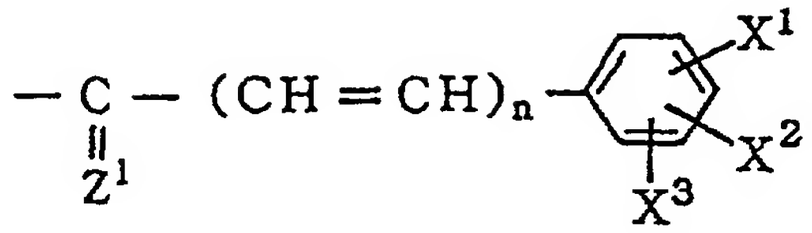
(1)



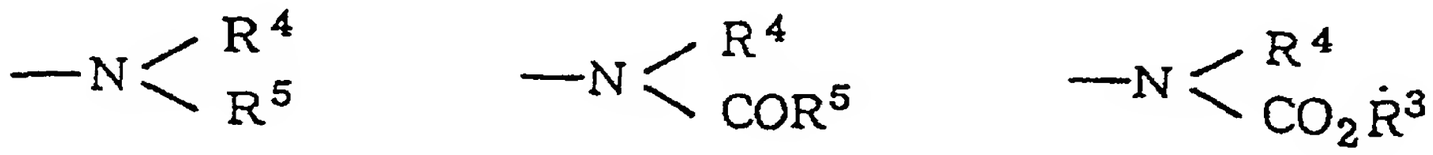
(2)

[In the formulas,
R is an alkyl group of $C_1 \sim C_4$;
R^1 is selected from the group consisting of ,

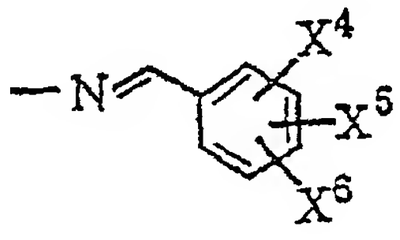
a.



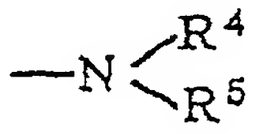
(X^1, X^2, and X^3 are independently a hydrogen atom, OH, OR^3 (R^3 is a linear or branched alkyl group of $C_1 \sim C_6$, $OCOR^3$ (R^3 is the same as above), CHO, NO_2,



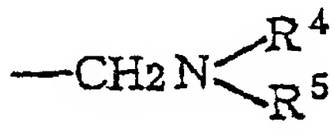
(R^4 and R^5 are independently a hydrogen atom, a linear or branched alkyl group of $C_1 \sim C_6$ (R^3 is the same as above)),



(X^4, X^5, and X^6 are independently a hydrogen atom, OR^3, or



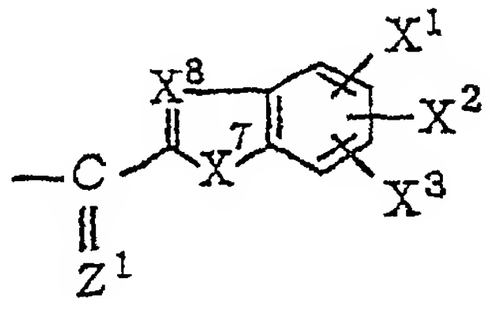
(R^3, R^4, and R^5 are the same as above)),



(R^4, and R^5 are the same as above),

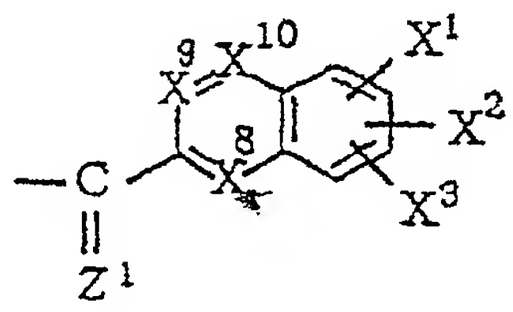
(R4, and R5 are the same as above), Z1 is O, S, or NR4 (R4 is the same as above), n is 0 ~ 2),

b.



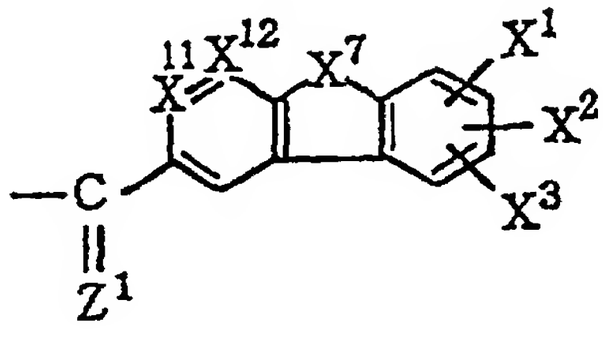
(X7 is O, S, or NH, X8 is CH or N (X1, X2, X3, and Z1 are the same as above)),

c.



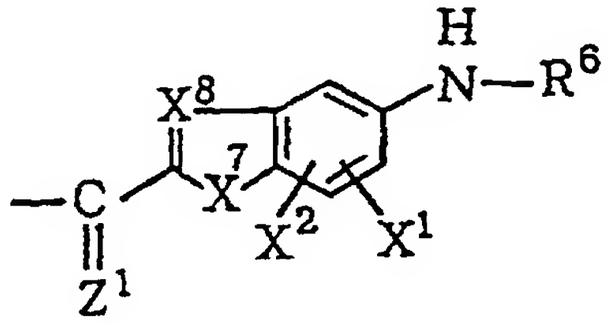
(X9, and X10 are independently CH or N (X1, X2, X3, X8, and Z1 are the same as above)),

d.



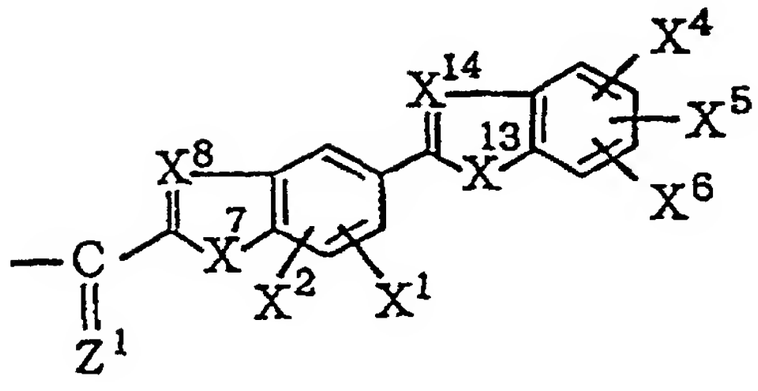
(X11, and X12 are independently CH or N (X1, X2, X3, X7, and Z1 are the same as above)),

e.



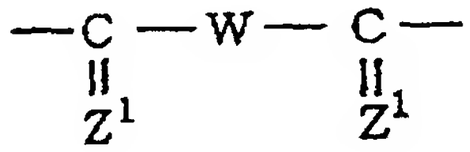
(R6 is represented by the above formula a, b, c, or d (X1, X2, X7, X8, and Z1 are the same as above)),

f.

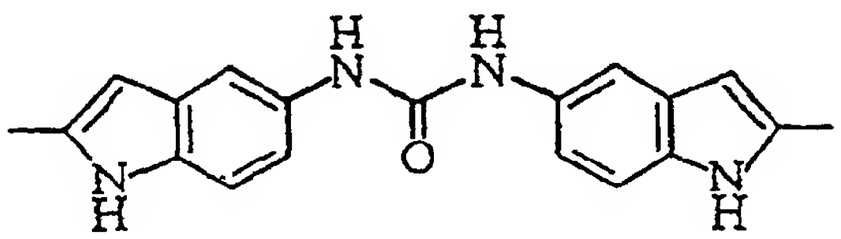


(X13 is O, S, or NH; X14 is CH or N (X1, X2, X4, X5, X6, X7, X8, and Z1 are the same as above)), and

g.

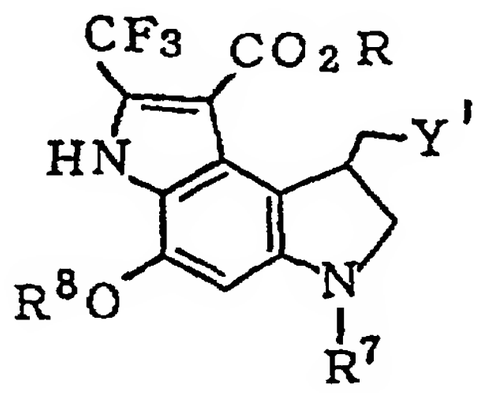


(W is $-(CH_2)_m-$, $-(CH_2)_m-Z^2-(CH_2)_n-$, or



(Z1 is the same as above), Z2 is S, O, or NH, and m and n are independently 0 ~ 16);
R2 is a hydrogen atom, a protecting group for the hydroxyl group, or a biologically decomposable substituent which is capable of giving a hydroxyl group by decomposition in an organism; and
Y is a halogen atom].

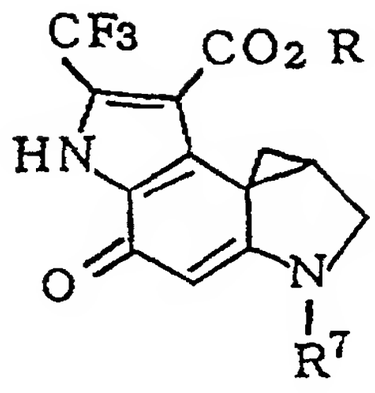
2. A trifluoromethylpyrroloindolecarboxylic acid ester intermediate represented by general formula (3):



(3)

(where R is a lower alkyl group of C_1 ~ C_4; R_7 is a hydrogen atom or a protective group for an amino group; R_8 is a hydrogen atom or a protective group for a hydroxyl group; Y1 is a hydroxyl group, a protective group for a hydroxyl group, or a halogen atom).

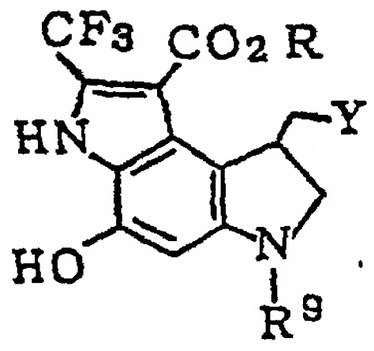
3. A trifluoromethylcyclopropapyrroloindole-carboxylic acid ester intermediate represented by general formula (4):



(4)

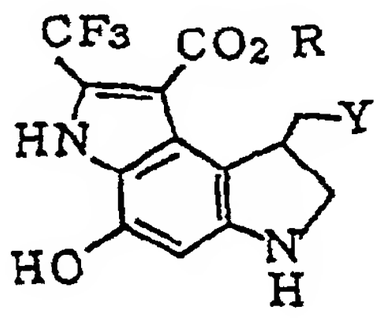
(where R is an alkyl group of $C_1 \sim C_4$; and R_7 is a hydrogen atom or a protective group for an amino group).

4. A process for the production of compound 1 of claim 1 wherein R^2 is a hydrogen atom, comprising the steps of deprotecting a compound represented by general formula (3a) below:



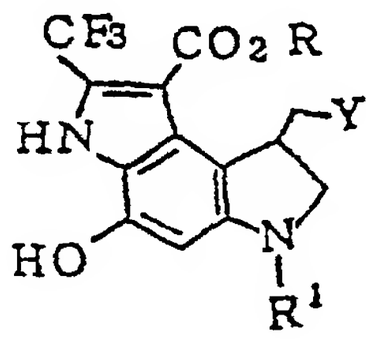
(3a)

(where R is a alkyl group of $C_1 \sim C_4$; R_9 is a protective group for an amino group; Y is as defined in claim 1 to form a compound represented by general formula (3b) or a salt thereof:



(3b)

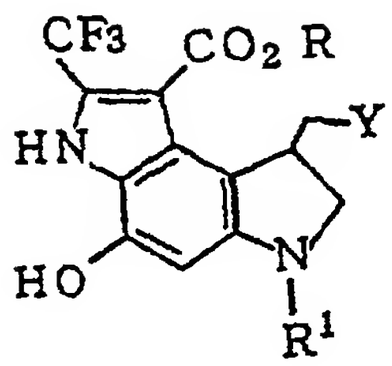
(where R and Y are the same as defined above.), and subsequently acylating or imidoylating the compound of formula (3b) to produce a compound represented by general formula (3c) below:



(3c)

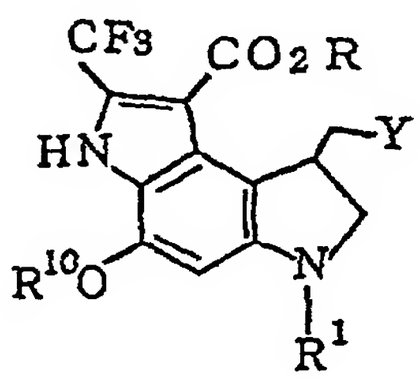
wherein R and Y are as defined above and R^1 is as defined in claim 1.

5. A process of protecting the hydroxyl group of a compound according to compound 1 of claim 1, wherein R^2 is a hydrogen atom represented by general formula (3c) with a biologicatty decomposable substituent which is capable of giving a hydroxyl group by decomposition in an organism:



(3c)

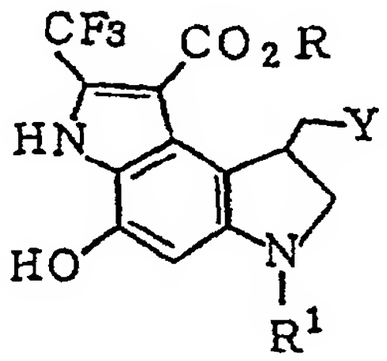
(where R, R^1 and Y are as defined in claim 1 to produce a compound of general formula (3d):



(3d)

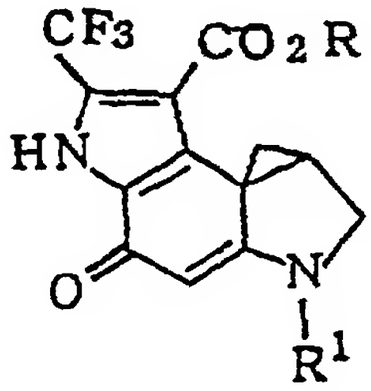
(where R^{10} is a biologically decomposable protective group for a hydroxyl group, and R, R^1 and Y are as defined above).

6. A process of ring closure of a compound represented by general formula (3c) in the presence of an organic or inorganic base:



(3c)

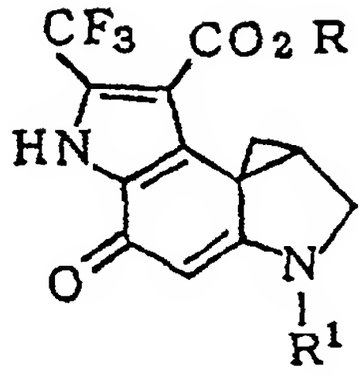
(where R, R^1 and Y are as defined in claim 1 to produce a compound of general formula (2) :



(2)

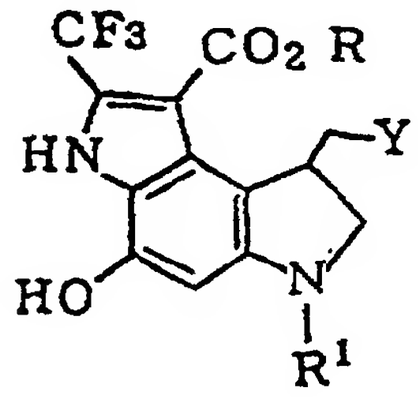
(where R and R^1 are as defined in claim 1.

7. A process of addition of an acid to a compound represented by general formula (2) :



(2)

where R and R^1 are as defined in claim 1 to produce a compound of general formula (3c):

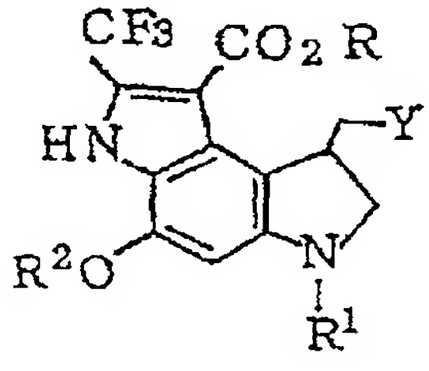


(3c)

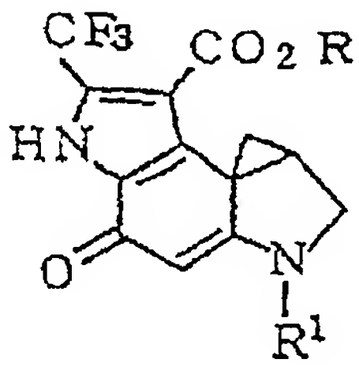
(where Y, R and R^1 are as defined in claim 1).

Patentansprüche

1. Trifluormethylpyrroloindolcarbonsäureester-Derivate, wiedergegeben durch die nachstehenden Formeln (1) und (2), optische Isomere davon und pharmazeutisch verträgliche Salze davon:

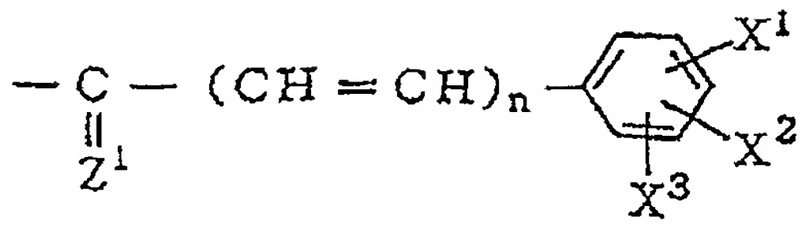


(1)

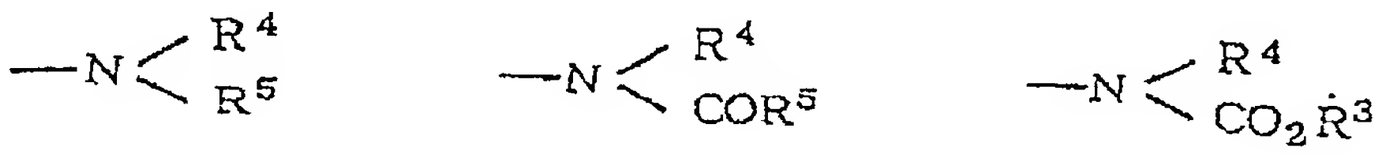


(2)

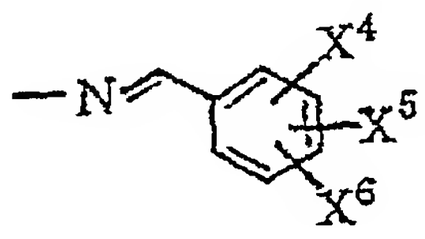
[wobei in den Formeln
R ein C_1-C_4-Alkylrest ist;
R^1 aus der Gruppe ausgewählt ist, bestehend aus

a. 

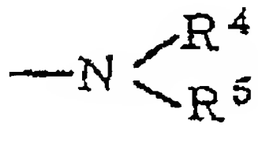
(wobei X^1, X^2 und X^3 unabhängig ein Wasserstoffatom, OH, OR^3 (wobei R^3 ein gerader oder verzweigter C_1-C_6-Alkylrest ist), $OCOR^3$ (wobei R^3 die vorstehend definierte Bedeutung hat), CHO, NO_2,



(wobei R^4 und R^5 unabhängig ein Wasserstoffatom, ein gerader oder verzweigter C_1-C_6-Alkylrest sind (wobei R^3 die vorstehend definierte Bedeutung hat)),



(wobei X^4, X^5 und X^6 unabhängig ein Wasserstoffatom, OR^3 oder

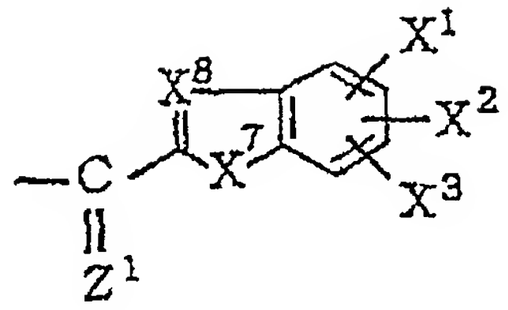


sind (wobei R^3, R^4 und R^5 die vorstehende Bedeutung haben)),

(wobei R^4 und R^5 die vorstehende Bedeutung haben),

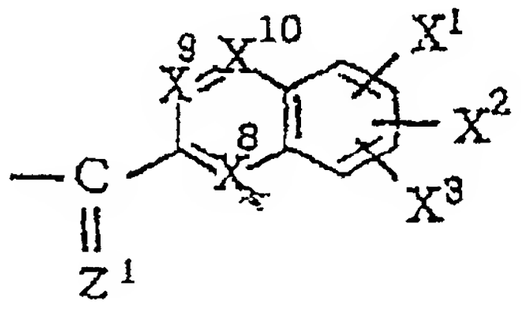
(wobei R^4 und R^5 die vorstehende Bedeutung haben) sind, Z^1 für O, S oder NR^4 steht (wobei R^4 die vorstehende Bedeutung hat), n die Bedeutung 0 - 2 hat,

b.



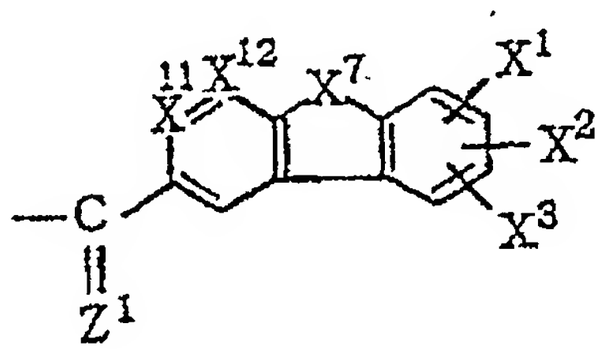
(wobei X^7 für O, S oder NH steht, X^8 für CH oder N steht (wobei X^1, X^2, X^3 und Z^1 die vorstehende Bedeutung haben)),

c.



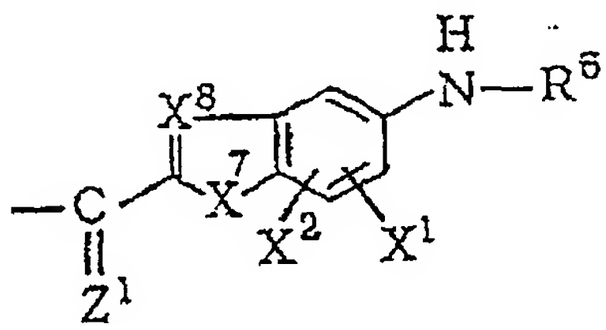
(wobei X^9 und X^{10} unabhängig für CH oder N stehen (wobei X^1, X^2, X^3, X^8 und Z^1 die vorstehende Bedeutung haben)),

d.



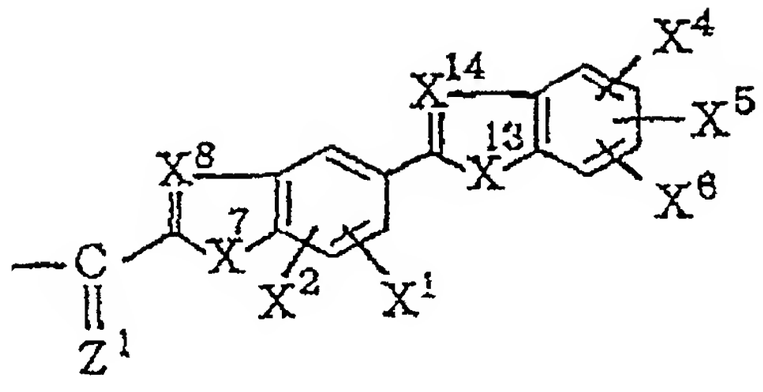
(wobei X^{11} und X^{12} unabhängig für CH oder N stehen (wobei X^1, X^2, X^3, X^7 und Z^1 die vorstehende Bedeutung haben)),

e.



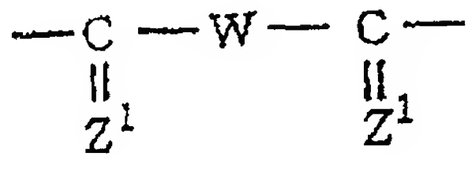
(wobei R^6 durch die vorstehende Formel a, b, c oder d wiedergegeben wird (wobei X^1, X^2, X^7, X^8 und Z^1 die vorstehende Bedeutung haben)),

f.

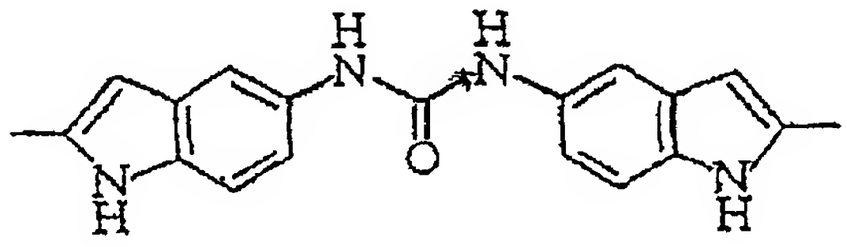


(wobei X^{13} für O, S oder NH steht; X^{14} für CH oder N steht (wobei X^1, X^2, X^4, X^5, X^6, X^7, X^8 und Z^1 die vorstehende Bedeutung haben)), und

g.

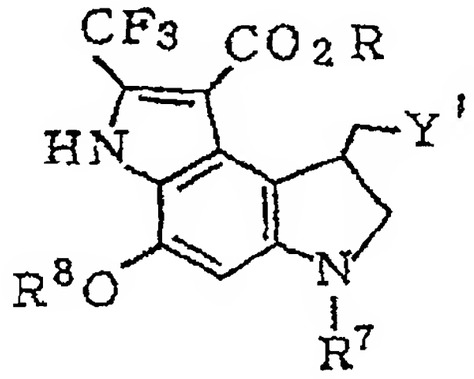


(wobei W die Bedeutung $-(CH_2)_m-$, $-(CH_2)_m-Z^2-(CH_2)_n-$ oder



hat (wobei Z^1 die vorstehend definierte Bedeutung hat), Z^2 für S, O oder NH steht und m und n unabhängig für 0 - 16 stehen);
R^2 ein Wasserstoffatom, eine Schutzgruppe für die Hydroxylgruppe oder ein biologisch abbaubarer Substituent ist, der bei der Zersetzung in einem Organismus eine Hydroxylgruppe ergeben kann; und
Y ein Halogenatom ist.]

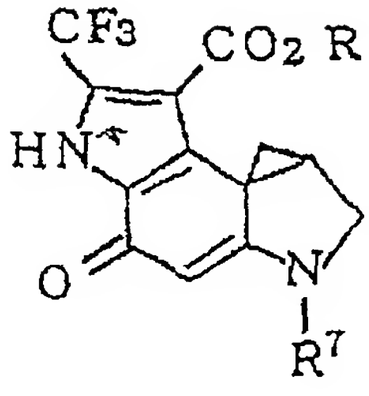
2. Trifluormethylpyrroloindolcarbonsäureester-Zwischenprodukt, wiedergegeben durch die allgemeine Formel (3):



(3)

(wobei R ein C_1-C_4-Niederalkylrest ist; R^7 ein Wasserstoffatom oder eine Schutzgruppe für eine Aminogruppe ist; R^8 ein Wasserstoffatom oder eine Schutzgruppe für eine Hydroxylgruppe ist; Y' eine Hydroxylgruppe, eine Schutzgruppe für eine Hydroxylgruppe oder ein Halogenatom ist.

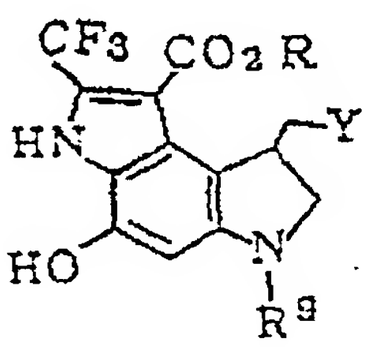
3. Trifluormethylcyclopropapyrroloindolcarbonsäureester-Zwischenprodukt, wiedergegeben durch die allgemeine Formel (4):



(4)

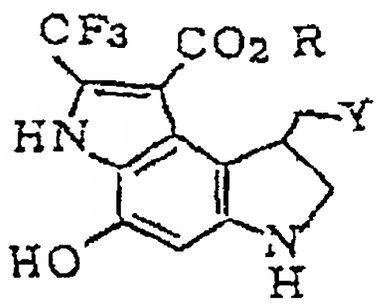
(wobei R ein C_1-C_4-Alkylrest ist und R^7 ein Wasserstoffatom oder eine Schutzgruppe für eine Aminogruppe ist.

4. Verfahren zur Herstellung der Verbindung 1 gemäß Anspruch 1, wobei R^2 ein Wasserstoffatom ist, umfassend die Schritte des Entfernens der Schutzgruppe von einer Verbindung, die durch die nachstehende allgemeine Formel (3a) wiedergegeben ist:



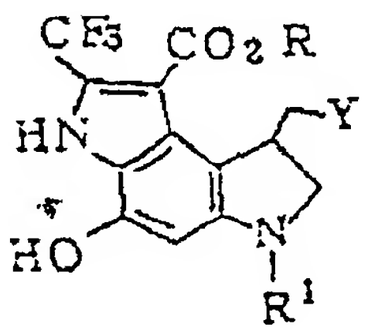
(3a)

(wobei R ein C_1-C_4-Alkylrest ist; R^9 eine Schutzgruppe für eine Aminogruppe ist; Y die im Anspruch 1 definierte Bedeutung hat; zur Herstellung einer Verbindung, die durch die nachstehende allgemeine Formel (3b) wiedergegeben ist, oder eines Salzes davon:



(3b)

(wobei R und Y die vorstehend definierte Bedeutung haben) und der anschließenden Acylierung oder Imidoylierung der Verbindung der Formel (3b) zur Herstellung einer Verbindung, die durch die nachstehende allgemeine Formel (3c) wiedergegeben ist:

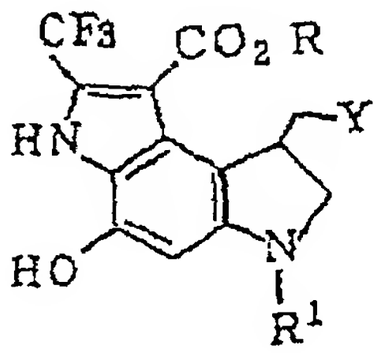


(3c)

wobei R und Y die vorstehend definierte Bedeutung haben und R^1 die im Anspruch 1 definierte Bedeutung hat.

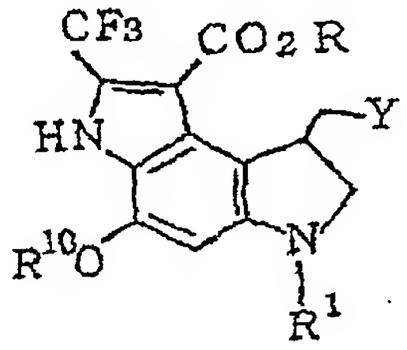
5. Verfahren zum Schützen der Hydroxylgruppe einer Verbindung gemäß Verbindung 1 nach Anspruch 1, wobei R^2 ein Wasserstoffatom ist, die durch die nachstehende allgemeine Formel (3c) wiedergegeben ist, mit einem biolo-

gisch abbaubaren Substituenten, der bei der Zersetzung in einem Organismus eine Hydroxylgruppe ergeben kann:



(3c)

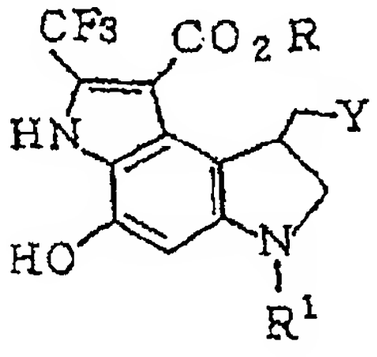
(wobei R, R^1 und Y die im Anspruch 1 definierte Bedeutung haben) zur Herstellung einer Verbindung der allgemeinen Formel (3d):



(3d)

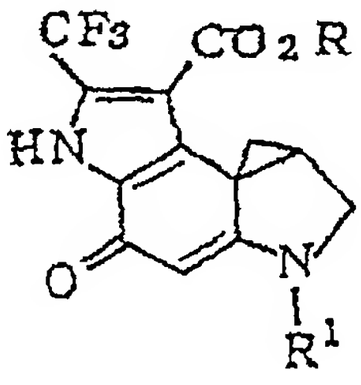
(wobei R^{10} eine biologisch abbaubare Schutzgruppe für eine Hydroxylgruppe ist und R, R^1 und Y die vorstehend definierte Bedeutung haben).

6. Verfahren zum Ringschluss bei einer Verbindung, die durch die allgemeine Formel (3c) wiedergegeben ist, in Anwesenheit einer organischen oder anorganischen Base:



(3c)

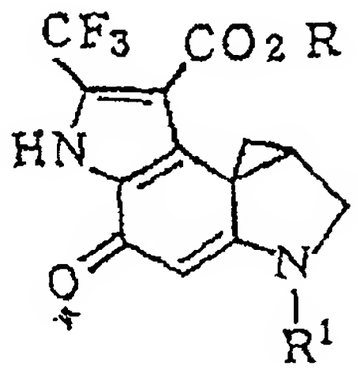
(wobei R, R^1 und Y die im Anspruch 1 definierte Bedeutung haben) zur Herstellung einer Verbindung der allgemeinen Formel (2):



(2)

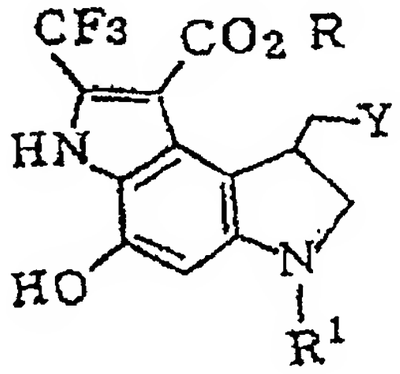
(wobei R und R^1 die im Anspruch 1 definierte Bedeutung haben).

7. Verfahren zur Addition einer Säure an eine Verbindung, die durch die allgemeine Formel (2) wiedergegeben ist:



(2)

wobei R und R^1 die im Anspruch 1 definierte Bedeutung haben, zur Herstellung einer Verbindung der allgemeinen Formel (3c):

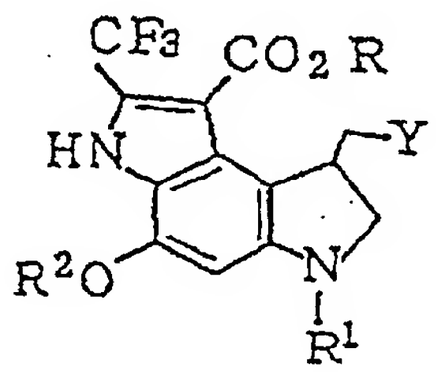


(3c)

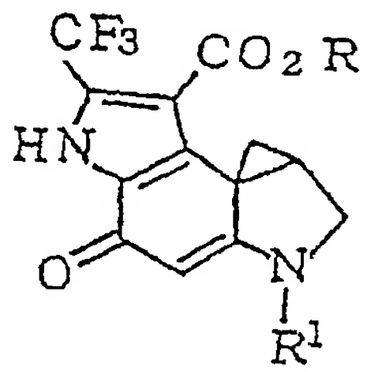
(wobei Y, R und R^1 die im Anspruch 1 definierte Bedeutung haben).

Revendications

1. Dérivés d'ester d'acide trifluorométhylpyrroloindolecarboxylique représenté par la formule générale (1) et (2) ci-dessous, les isomères optiques de ceux-ci et les sels pharmaceutiquement acceptables de ceux-ci:

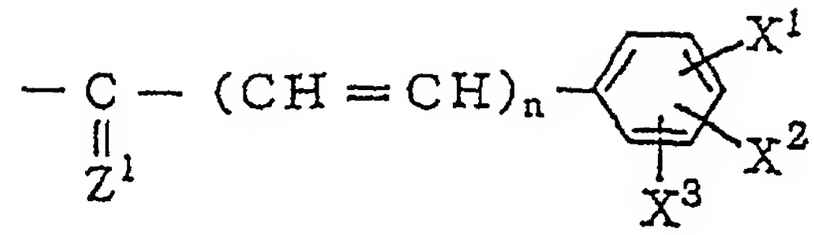


(1)

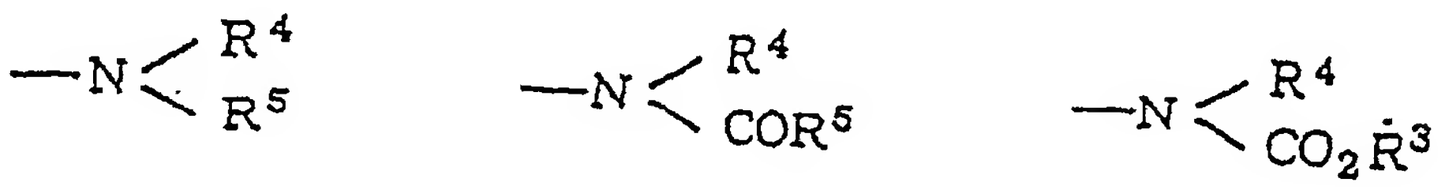


(2)

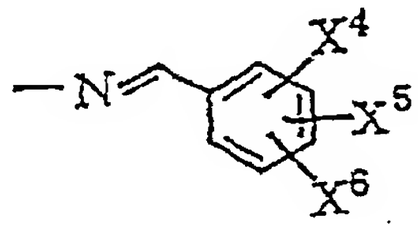
[Dans les formules,
R est un groupe alkyle en C_1-C_4;
R^1 est choisi dans le groupe constitué par

a. 

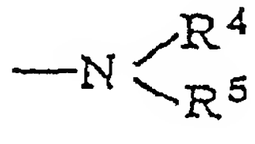
(X^1, X^2, et X^3 sont indépendamment un atome d'hydrogène, OH, OR^3 (R^3 est un groupe alkyle linéaire ou ramifié en C_1-C_6), $OCOR^3$ (R^3 est le même que ci-dessus), CHO, NO_2,



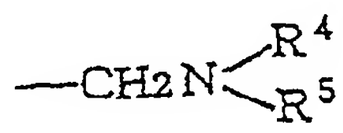
(R^4 et R^5 sont indépendamment un atome d'hydrogène, un groupe alkyle linéaire ou ramifié en C_1-C_6 (R^3 est le même que ci-dessus)),



(X^4, X^5 et X^6 sont indépendamment un atome d'hydrogène, OR^3 ou



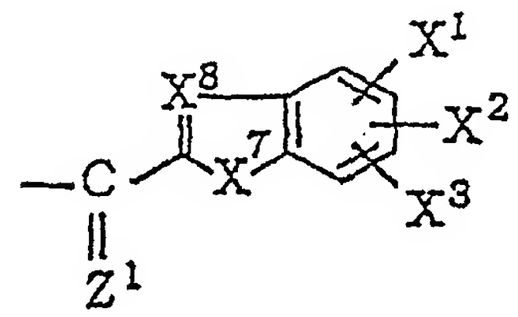
(R^3, R^4 et R^5 sont les mêmes que ci-dessus)),



(R^4 et R^5 sont les mêmes que ci-dessus),

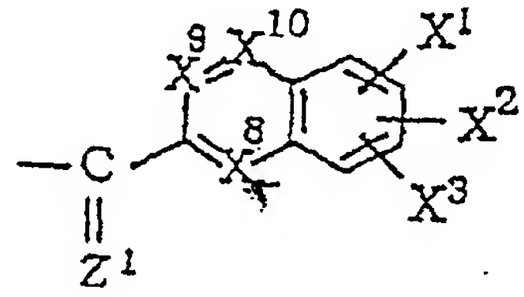
(R^4 et R^5 sont les mêmes que ci-dessus), Z^1 est O, S ou NR^4 (R^4 est le même que ci-dessus), n est 0 - 2),

b.



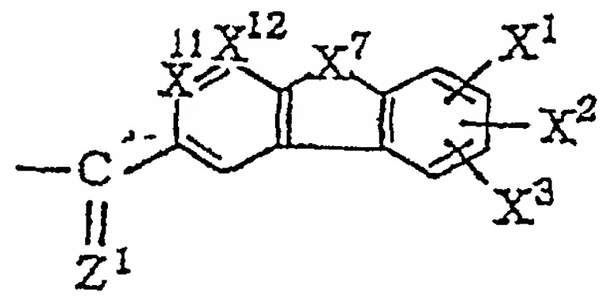
(X^7 est O, S ou NH, X^8 est CH ou N (X^1, X^2, X^3 et Z^1 sont les mêmes que ci-dessus)),

c.



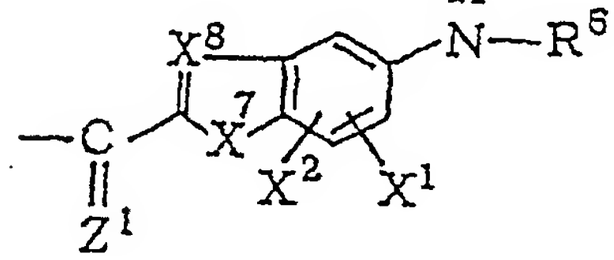
(X^9 et X^{10} sont indépendamment CH ou N (X^1, X^2, X^3, X^8, et Z^1 sont les mêmes que ci-dessus)).

d.



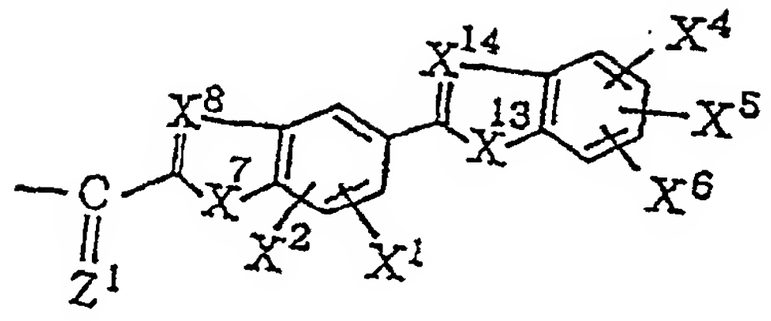
(X^{11} et X^{12} sont indépendamment CH ou N (X^1, X^2, X^3, X^7, et Z^1 sont les mêmes que ci-dessus)),

e.



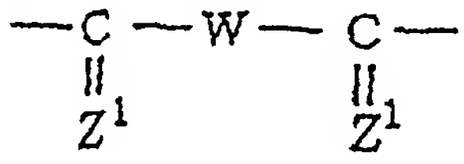
(R^6 est représenté par la formule a, b, c, ou d ci-dessus (X^1, X^2, X^7, X^8, et Z^1 sont les mêmes que ci-dessus)),

f.

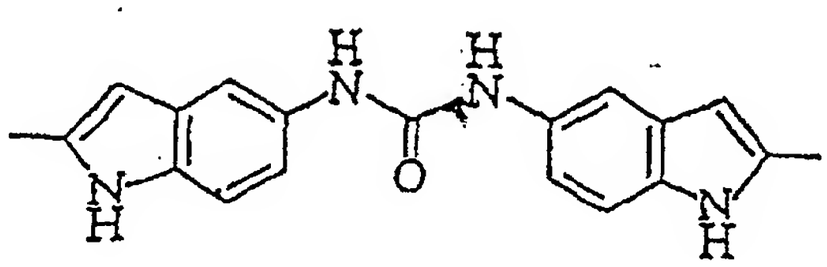


(X13 est O, S ou NH; X14 est CH ou N (X1, X2, X4, X5, X6, X7, X8 et Z1 sont les mêmes que ci-dessus)), et

g.

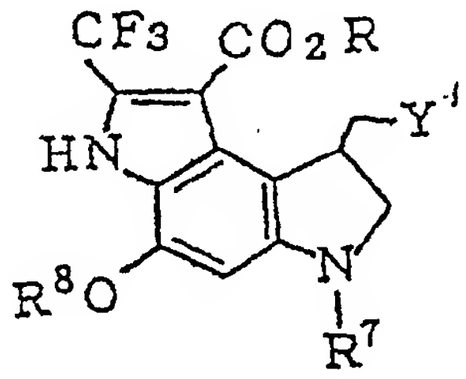


(W est - $(CH_2)_m$-, -$(CH_2)_m$-Z^2-$(CH_2)_n$-, ou



(Z^1 est le même que ci-dessus), Z^2 est S, O, ou NH et m et n sont indépendamment 0 - 16);
R^2 est un atome d'hydrogéne, un groupe protecteur pour le groupe hydroxyle, ou un substituant pouvant se décomposer biologiquement qui est capable de donner un groupe hydroxyle par décomposition dans un organisme; et
Y est un atome d'halogène].

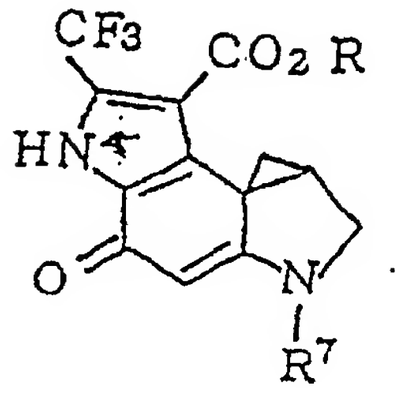
2. Intermédiaire d'ester d'acide trifluorométhylpyrroloindolecarboxylique représenté par la formule générale (3) :



(3)

(où R est un groupe alkyle inférieur de C_1-C_4; R^7 est un atome d'hydrogène ou un groupe protecteur pour un groupe amino; R^8 est un atome d'hydrogène ou un groupe protecteur pour un groupe hydroxyle; Y^1 est un groupe hydroxyle, un groupe protecteur pour un groupe hydroxyle ou un atome d'halogène).

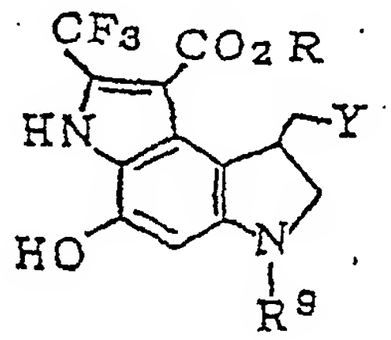
3. Intermédiaire d'ester d'acide trifluorométhylcyclopropapyrroloindolecarboxylique représenté par la formule générale (4) :



(4)

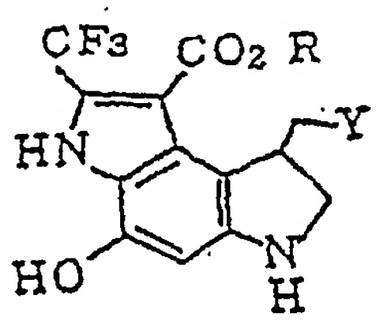
(où R est un groupe alkyle en C_1-C_4; et R^7 est un atome d'hydrogène ou un groupe protecteur pour un groupe amino).

4. Procédé pour la préparation d'un composé 1 de la revendication 1 dans lequel R^2 est un atome d'hydrogène, comprenant les étapes consistant à déprotéger un composé représenté par la formule générale (3a) ci-dessous :



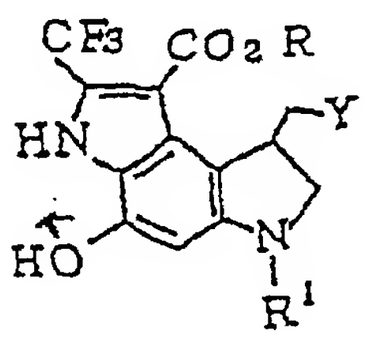
(3a)

(où R est un groupe alkyle en C_1-C_4; R^9 est un groupe protecteur pour un groupe amino; Y est tel que défini dans la revendication 1), pour former un composé représenté par la formule générale (3b) ou un sel de celui-ci :



(3b)

(où R et Y sont les mêmes que définis ci-dessus), et ultérieurement à acyler ou à imidoyler le composé de formule (3b) pour produire un composé représenté par la formule générale (3c) ci-dessous :

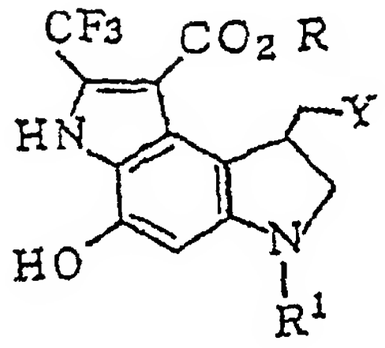


(3c)

où R et Y sont tels que définis ci-dessus et R^1 est tel que défini dans la revendication 1.

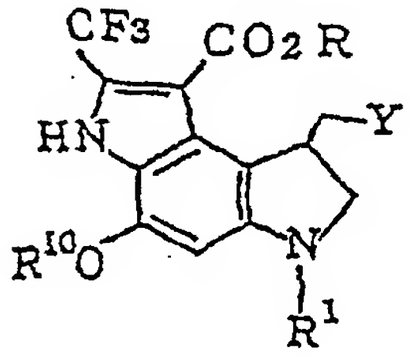
5. Procédé de protection du groupe hydroxyle d'un composé conforme au composé 1 de la revendication 1, dans lequel R^2 est un atome d'hydrogène, représenté par la formule générale (3c) avec un substituant pouvant se

décomposer biologiquement qui est capable de donner un groupe hydroxyle par décomposition dans un organisme :



(3c)

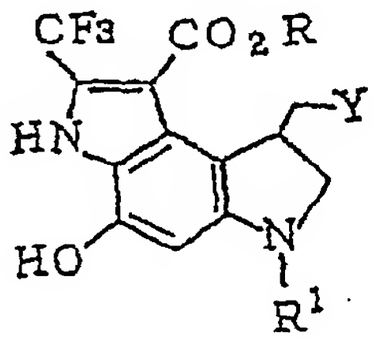
(où R, R^1 et Y sont tels que définis dans la revendication 1) pour produire un composé de formule générale (3d) :



(3d)

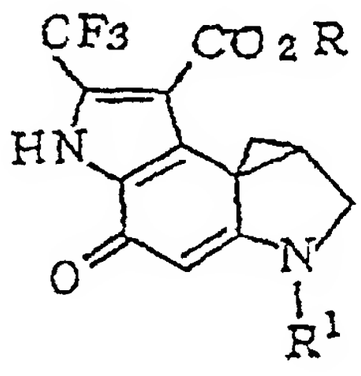
(où R^{10} est un groupe protecteur pouvant se décomposer biologiquement pour un groupe hydroxyle, et R, R^1 et Y sont tels que définis ci-dessus).

6. Procédé de fermeture de cycle d'un composé représenté par la formule générale (3c) en présence d'une base organique ou inorganique :



(3c)

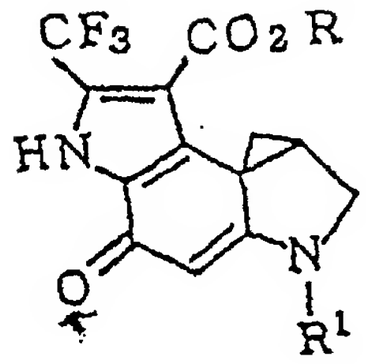
(où R, R^1 et Y sont tels que définis dans la revendication 1) pour produire un composé de formule générale (2) :



(2)

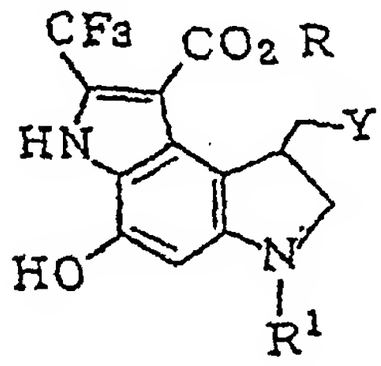
(où R et R^1 sont tels que définis dans la revendication 1).

7. Procédé d'addition d'un acide à un composé représenté par la formule générale (2) :



(2)

où R et R^1 sont tels que définis dans la revendication 1, pour produire un composé de formule générale (3c) :



(3c)

(où Y, R et R^1 sont tels que définis dans la revendication 1).